STUDY ON THE PREVALENCE OF GLUTAMIC ACID DECARBOXYLASE ANTIBODIES IN TYPE 1 DIABETIC CHILDREN

Dissertation submitted for

M.D DEGREE EXAMINATION

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INSTITUTE OF CHILD HEALTH AND

HOSPITAL FOR CHILDREN

MADRAS MEDICAL COLLEGE

CHENNAI

CERTIFICATE

This is to certify that the dissertation titled, **"Study on the prevalence of glutamic acid decarboxylase antibodies in type 1 diabetic children"** submitted by Dr.R. Nagalekshmi, to the Faculty of Pediatrics, The Tamilnadu Dr.M.G.R Medical University, Chennai, in partial fulfilment of the requirements for the award of M.D. Degree (Pediatrics) is a bonafide research work carried out by her under our direct supervision and guidance.

Prof.Dr. R.Vimala, M. D,
Dean,
Madras Medical College,
Chennai – 600003

Prof.Dr.S. Sundari. M. D., DCH
Director and Superintendent,
Institute of Child Health and
Hospital for Children,
Chennai – 600008

Prof. Dr .C. Subbulakshmi M.D., DCH.,
Professor of paediatrics,
Unit Chief, Research Guide,
Institute of Child Health

DECLARATION

I, **Dr.R. Nagalekshmi**, solemnly declare that the dissertation titled "Study on the prevalence of glutamic acid decarboxylase antibodies in Type 1 Diabetic children" has been prepared by me.

This is submitted to the Tamilnadu Dr. M.G.R. Medical University, Chennai in partial fulfilment of the rules and regulations for the M.D. Degree Examination in Pediatrics.

Dr.R. Nagalekshmi

Place : Chennai

Date

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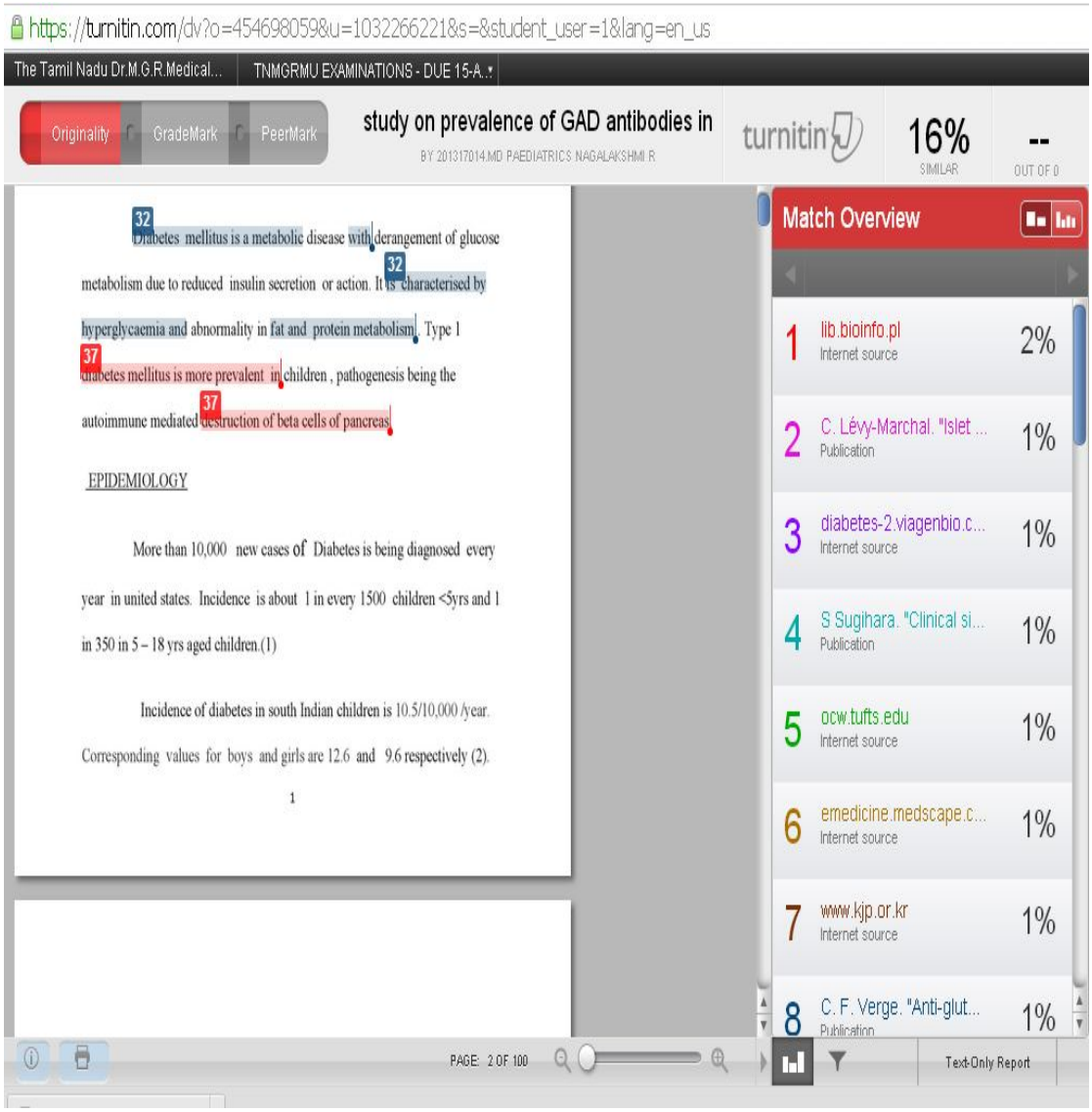
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EPIDEMIOLOGY
More than 10,000 new cases of Diabetes is being diagnosed every year in united states. Incidence is about 1 in every 1500 children <5yrs and 1 in 350 in 5 – 18 yrs aged children.(1)
Incidence of diabetes in south Indian children is 10.5/10,000 /year. Corresponding values for boys and girls are 12.6 and 9.6 respectively (2).
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STUDY ON PREVALENCE OF
GAD ANTIBODIES IN
TYPE 1 DIABETIC CHILDREN

INTRODUCTION

Diabetes mellitus is a metabolic disease with derangement of glucose metabolism due to reduced insulin secretion or action. It is characterized by hyperglycaemia and abnormalities in fat and protein metabolism. Type 1 diabetes mellitus is more prevalent in children, pathogenesis being the autoimmune mediated destruction of beta cells of pancreas.

EPIDEMIOLOGY

More than 110,000 new cases of Diabetes is being diagnosed every year in united states. Incidence is about 1 in every 1,000 children <5yrs and 1 in 150 in 5 – 19 yrs aged children.[1]

Incidence of diabetes in south Indian children is 10.52/1,00,000/year. Corresponding values for boys and girls are 12.6 and 8.4 respectively.[2]

1

CONTENTS

Abstract

Background

Diabetic mellitus is a chronic disease in children. Autoimmunity is the principle etiology of this disorder. This is established by presence of auto antibodies . There are various autoantibodies like GAD , ICA 512 , IAA.There is a wide variation in prevalence of GAD antibodies in various population and there are few studies in our population so we proceeded with this study

Materials and methods

All newly diagnosed type 1 diabetic children between the age of 1-12years attending our diabetic clinic were enrolled in our study. A total of 50 patients were studied. Diagnosis was confirmed by clinical criteria. Serum samples of them were collected and analysed for GAD antibodies by ELISA method. HbA1c and insulin requirement was also taken to compare with autoimmunity.

Results

The prevalence of GAD antibodies in our study group was 42% . The disease was more prevalent in children above 10 years. There was no significant metabolic derangements when comparing positivity for GAD antibodies. Large sample of patients can be analysed by multicentric study

Key word- new onset diabetic children , GAD antibodies, autoimmunity.

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EPIDEMIOLOGY

More than 10,000 new cases of Diabetes is being diagnosed every year in United States. Incidence is about 1 in every 1500 children <5yrs and 1 in 350 in 5 – 18 yrs aged children.[1]

Incidence of diabetes in south Indian children is 10.5/10,000 /year. Corresponding values for boys and girls are 12.6 and 9.6 respectively [2]. There are two peaks in age of presentation, first at 5 – 7yrs and then at puberty. Both sexes are equally affected . There is seasonal variation with more cases reported in winter months. Monozygotic twins have a 60%

risk of developing diabetes. In contrast, dizygotic twins have only an 8% risk of concordance.[3]

The risk of diabetes in children with maternal history of diabetes is 2-3% and 5-6% [3] for children with paternal history of type1DM. But 85% of children have no family history.

ETIOLOGY

HLA /MHC encoded susceptibility to type 1 DM

In 95%, type1 DM is due to influence of environmental factors with increased incidence in genetically susceptible individuals. Evidence suggest Human leukocyte antigen (HLA) class II molecules DR3 and DR4 are strongly associated with type 1 DM. More than 90% of whites with type 1 diabetes mellitus express DR3 compared to 50-60% in the general population. Patients expressing DR3 are also at risk for developing other autoimmune endocrinopathies and celiac disease . Absence of aspartic acid at position 57 within DQ beta chain and absence of arginine at 52 in DQ alpha chain increases the risk by 100 times.

Role of HLA Class1

HLA complex especially HLA –A and HLA –B have more significance. But HLA -39 confers high risk for type 1 DM.

PTPN22 (Lymphoid Tyrosine Phosphatase)

Single nucleotide polymorphisms in the gene located on chromosome 1p13 that encodes lymphoid tyrosine phosphatase is associated with type1 DM.

CTLA -4

Cytotoxic T lymphocyte antigen -4 located on chromosome 2q is associated with type 1 DM.

Interleukin -2 Receptor

Interleukin -2 receptor SNP near the gene expressing IL-2 receptor is associated with diabetes.

Interleukin -1 Receptor

Inhibition of activation of IL - 1 receptor is associated with type 1 DM.

Interferon induced helicase [(4)]

This gene protects the host from viral infections and variation results in diabetes, thus demonstrating the role of virus in this disease.

CYP27B1

A subfamily of cytochrome p450, encodes vitamin D 1 alpha hydroxylase. This gene is associated with type1DM. Thus demonstrating the role of vitamin D in diabetes.

Autoimmunity

Development of antibodies and T lymphocytes targeted to beta cells and release of cytokines within pancreatic islets results in destruction of beta cells. Thus Beta cell destruction is due to combination of direct CD8T cell attack and cytotoxity from release of free radicals and cytokines like IL-1, TNFα, TNFβ, and IFN gamma released from macrophages and T cells . Greater than 80% of patients have beta cell antibodies at the time of diagnosis. The autoantibodies in DM includes insulin autoantibodies, 65-kd isoform of glutamic acid decarboxylase antibodies, insulinoma associated protein - IA2,ICA512 autoantigen. The presence of antibodies varies with age and decreases with longer duration of disease. Persons with positive ICA and positive family history of diabetes have high predilection for developing diabetes. Risk being higher in patients with multiple antibodies.

Glutamic Acid Decarboxylase

This 64 kda islet autoantigen is one of the important assay for islet autoantibodies. Mapping epitopes recognised by GAD 65 autoantibodies indicate that entire surface of molecule is target for GAD autoantibodies. This proves GAD 65 is immunogen in beta cell destruction which is expressed in all islet cell .Both GAD 65 and GAD 67 present in cytoplasmic microvesicles of neurons and in endocrine. GAD 65 is more pronounced in females than male in children less than 12 years .GAD 65 is associated with rapid onset of type 1 diabetes. ‘Prevalence of ICA and IAA decreases with increasing age of onset.

ICA 512 (IA-2beta)

ICA-512 antibodies homologous to tyrosine phosphatase like molecule is expressed in neuronal and endocrinal tissue. Molecules associated with islet secretary granules detected by ELISA autoantibodies react with intracytoplasmic portion of the molecule then secretory granules fuse with plasma membrane. ICA 512 autoantibodies are most specific form of antibodies. ICA 512 may be only autoantibody in pre diabetic phase

Insulinoma Associated Antibodies

This is a nonspecific antibody directed against beta cell, detected in 60% of patients.

Insulin Autoantibodies

Autoantibody targeted to insulin. It is the only antibody thought to be highly specific for beta cells. Detected in about 50% of type 1 diabetic children.

Environmental Factors

Autoantibodies are detected after mumps, measles, chickenpox, coxsackie and rotavirus infection. Breast feeding is protective and early exposure to cows milk increases the risk of type 1 DM. Perinatal factors like preeclampsia, Lscs, RDS, birth weight, gestational age, birth order and maternal age increases the risk.

Congenital Rubella Syndrome

Prenatal rubella infection is associated with autoimmunity in 70% of children which increases the risk of developing type 1 DM later. 70% of children with rubella acquired after birth have no risk.

Enteroviruses

There are case reports which show association between enterovirus infection and subsequent development of type 1 diabetes.

Mumps Virus

Mumps infection leads to development of beta cell autoimmunity with high frequency of type 1 diabetes.

Immunisation

Immunisation against mumps and pertusis decreases the risk of type 1 diabetes

Other Autoantibodies

One fourth of type 1 diabetic patient have thyroid autoantibodies especially antibodies against peroxidose or thyroglobulin. They may later develop overt disease like hashimotos thyroiditis resulting in hypothyroidism. Thus it becomes necessary to do thyroid function test yearly once.

Celiac Disease

Celiac disease is seen in type 1 diabetic patients and is asymptomatic. It is associated with HLA DR3 and DR4 and endomysial autoantigen such as tissue transglutaminase. Transglutaminase

autoantibody is present in one third of type 1 diabetic patients. Wheat rich diet in diabetic patients increases the burden, since celiac disease is an immune mediated disorder to gliadin present in wheat.

Addisons Disease

Type 1 diabetic patients are prone to develop antibodies to 21hydrooxylase and thus develop addisons disease. Insulin requirement decreases in diabetics with coexistent addisons disease.

Other Autoimmune Disorders

Myasthenia gravis, graves disease, juvenile rheumatoid arthritis, pernicious anaemia can also occur.

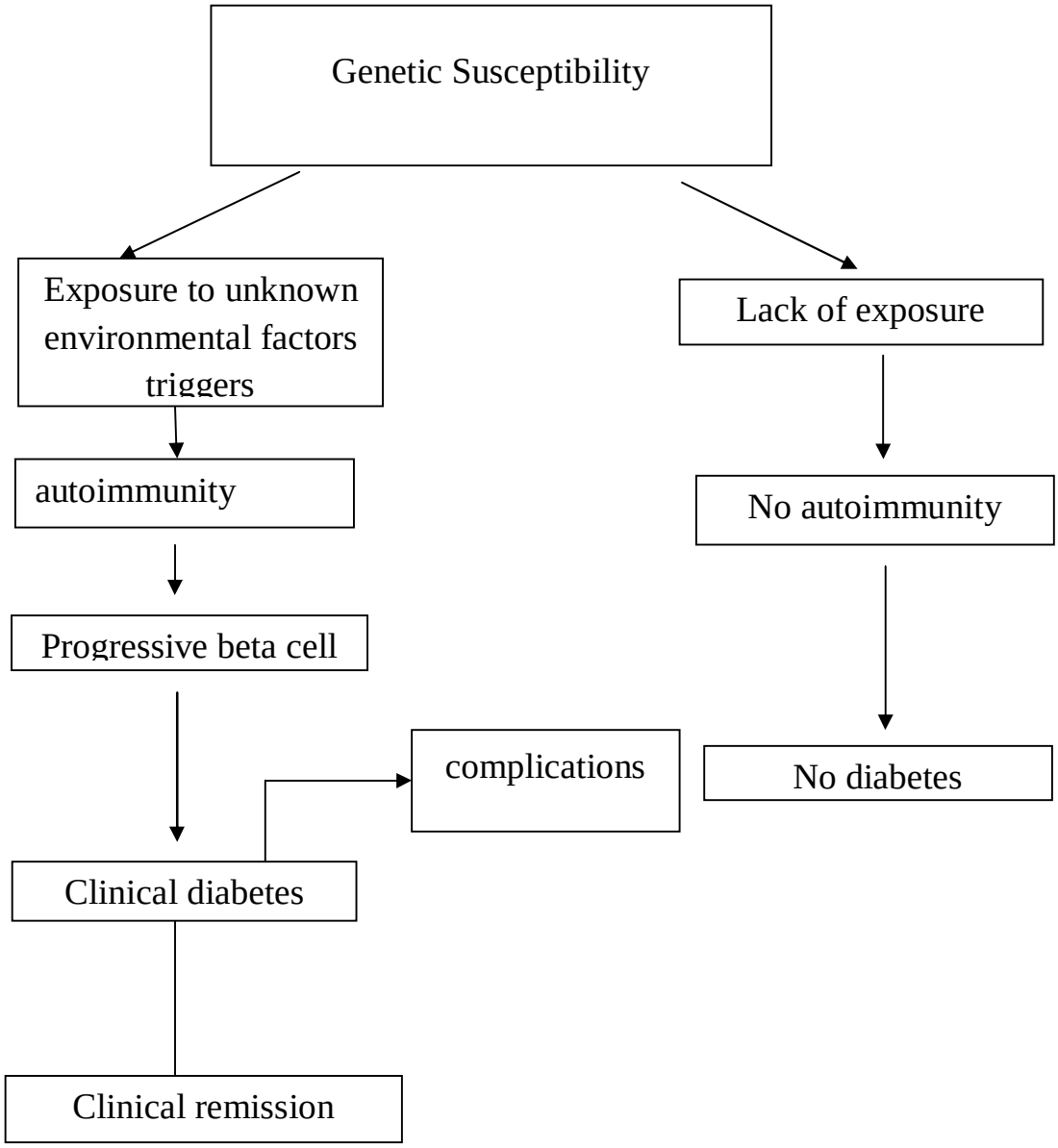
Autoimmune Poly Endocrine Syndromes

18 % of patient with autoimmune polyendocrine syndrome -1 (mucocutaneous candidiasis, addisons disease and hypothyroidism) develop type 1 diabetes, which is more common in patients with glutamic acid decarboxylase antibodies.

PATHOGENESIS

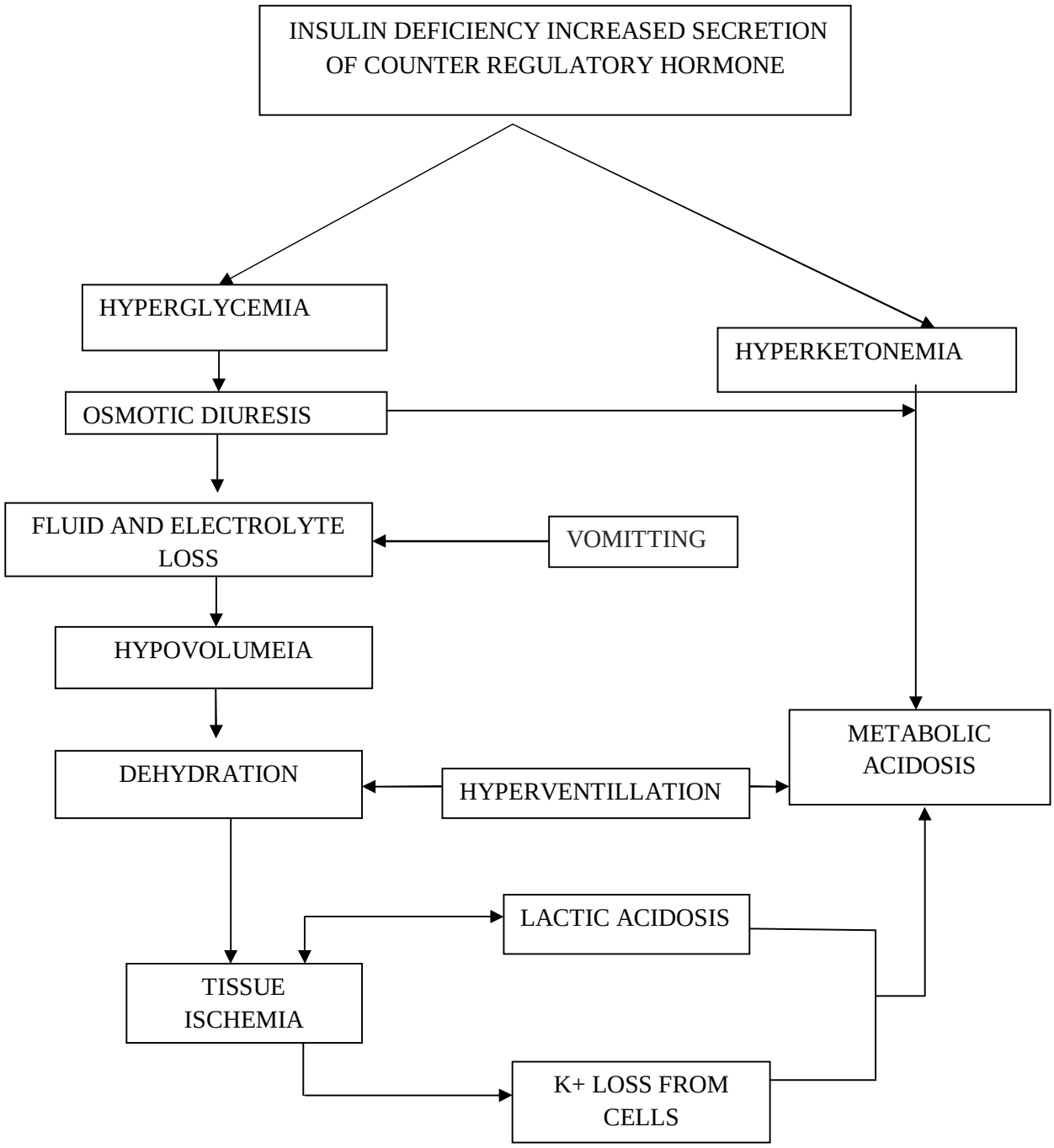
Immune dysregulation, influenced by genetic susceptibility and environmental modifiers, leads to development of autoantibodies against various islet cell components, including glutamic acid decarboxylase antibodies (GAD-65), islet cell antibodies (ICA512/IA-2) and insulin antibodies (IAA). Presence of multiple autoantibodies is a predictor of future DM Primary pathogenesis is Beta cell destruction. It is a T-cell mediated process, as evidenced by the presence of intense insulinitis in newly diagnosed patients. Rapid destruction occurs in younger individuals and slower in older individuals. Autoimmune disorders including Graves' disease, Addison's disease and autoimmune polyendocrine syndromes are associated with diabetes.

Natural history of type 1DM



Pathogenesis of Diabetic ketoacidosis

Insulin is a anabolic hormone secreted when there is rise in blood glucose level. Receptor mediated mechanism allow the uptake of glucose into the cell which stimulates glycogen synthesis, inhibits glucogenesis and glycogenolysis and increases lipid synthesis from triglycerides and glycerol. Insulin favours storage of lipid in adipose tissue, increases uptake of amino acid, protein and glycogen synthesis . In absence of insulin serum glucose cannot be used by peripheral tissue because of dependence of peripheral tissue glucose transporters on insulin. Hepatic glycogenolysis and gluconeogenesis are stimulated resulting in hyperglycemia. When serum glucose level exceeds renal threshold, osmotic diuresis occurs and it leads to significant urinary loses of fluids and potassium, sodium, calcium, phosphorus and magnesium. Hyperglycemia and reduced peripheral glucose uptake with urinary water losses, leads to dehydration and hyperosmolarity. Increased lipolysis in adipose tissue,fatty acid oxidation in the liver and proteolysis in muscle leads to accumulation of ketones betahydroxybutrate and acetoacetate and leads to metabolic acidosis.


INSULIN DEFICIENCY INCREASED SECRETION OF COUNTER REGULATORY HORMONE
HYPERGLYCEMIA
HYPERKETONEMIA
OSMOTIC DIURESIS
FLUID AND ELECTROLYTE LOSS
VOMITTING
HYPOVOLUMEIA
METABOLIC ACIDOSIS
DEHYDRATION
HYPERVENTILLATION
LACTIC ACIDOSIS
TISSUE ISCHEMIA
K+ LOSS FROM CELLS

Classification of Diabetes Mellitus

Neonatal Diabetes

Transient

Permanent

Genetic Defects in Insulin Action

Rabson mendenhall syndrome

Donahue syndrome(Leprechauniusm diabetes)

Liprotrophic diabete

Type 1 Diabetes

Immune mediated

Slowly progressive type 1 diabetes

Non Immune Mediated

Type 2 diabetes

Monogenic diabetes

Atypical diabetes

Maturity Onset Diabetes of Youth

MODY 1

MODY 2

MODY3

MODY4

MODY5

MODY6

Mitochondrial diabetes

Disease of Exocrine Pancreas

Cystic fibrosis

Neoplasia

Pancreatitis

Haemochromatosis

Endocrinopathies

Acromegaly

Cushings syndrome

Glucoginoma, pheochromocytoma

Somatostatinoma

Drug Induced

corticosteroid

pentamidine

thiazides

beta adrenergic agonist

antipsycotic

infections /critical illness

Uncommon Forms of Immune Mediated Diabetes

stiffman syndrome

type B insulin resistance

Autoimmune hypoglycaemia

Genetic Syndrome Associated with Diabetes

Downs syndrome

Klienfelter syndrome

Turner syndrome

Wolfram syndrome

Huntington chorea

Laurence moon biedl syndrome

Myotonic dystrophy [5]

Clinical Features

Symptoms of hyperglycemia includes

polyuria

polydypsia,

polyphagia,

weight loss,

easy fatiguability,

enuresis in previously toilet trained child

vaginal candidiasis in prepubertal girls

Emergency presentation in DKA includes

dehydration,

vomiting

hyperventilation (kussamul respiration)

altered sensorium,

abdominal pain,

shock,

hypotension and

hypoglycemia

Diagnosis

According to ISPAD guidelines

Criteria for diagnosis of diabetes mellitus

1. Symptoms of diabetes plus casual glucose concentration>11.1mmol/l (200mg/dl)
2. Fasting plasma glucose > 7mmol/l(126 mg/dl)
3. 2 hr postprandial glucose >11.1mmol/l(200mg/dl) during an OGTT (the test to be done as per WHO using a glucose load of 75g dissolved in water) [6]

Glycosylated Haemoglobin

Glycosylated haemoglobin is a measure of long term glycemic control

This represents fraction of haemoglobin that is nonenzymaticaly attached to glucose. Formation of glycosylated haemoglobin is a slow process. Depends on blood sugar and continues irreversibly throughout

lifespan of RBC’s .High HbA1c means high blood sugar and increased exposure of RBCs to glycemic level.

It reflects glucose concentration in preceeding 2-3 months. Index of long term glycemic control. Persistently low value of HBA1C indicates good glycemic control.

It is spuriously elevated in thalassemia and in conditions with foetal haemoglobin, and is reduced in sickle cell anaemia. Usually less than 6%. Value 6-7.9 % means good metabolic control, 8-9.9 indicates fair control, values >10 means poor control.

The measurement of c- peptide is used to differentiate type 1 from type2 Diabetes.

The etiology of autoimmunity is confirmed by detection of anti beta cell antibodies like GAD,IA2, ICA-2,IA

There are various methods of detection

ELISA,

Radioimmunoassay

Radioligand assay

To detect autoantibodies - ELISA with a fusion protein thioredoxin produced in E. Coli as antigen is used . c- ELISA showed high specificity. p-ELISA is both sensitive and specific .

Microtiter plate assay for detection of GAD antibodies in type 1 diabetic patient by using the varelisa anti GAD 11 ELISA, is more sensitive and specific.

GAD -65 antibodies can be detected by simple quantitative immunoprecipitation radioligand assay using S35 methionine –labelled human islet GAD 65 as antigen . Using this assay it is easy to detect 77% of GAD antibody positive patient at onset of disease.

Investigations in DKA

random blood sugar,

urine ketones,

serum electrolytes,

arterial blood gas analysis,

blood and urine culture,

urine albumin,

renal function test,

radioimaging and ultrasound abdomen

and investigations to rule out sepsis should be done .

Lab Findings in Diabetic Ketoacidosis

Due to hyperglycemia

Glycosuria

Ketonuria

Ketoacidosis

Glucosuria

Ketonuria /ketonemia

Anion gap acidosis

Decreased pH

Insulin resistance

high insulin

increased c-peptide

elevated adrenal androgens

elevated liver enzymes

Management

The principle goals are:

1. metabolic stabilisation
2. avoid acute complications
3. Prevention of parent and child isolation
4. Identification and treatment of behavioural dilemmas
5. education of family to care the child after stabilisation
6. integration of diabetes routines into school,day care,and family activities
7. maintenance of normal growth and development [7]

Treatment varies with severity of illness at onset . Treatment varies depending on the presence or absence of dehydration. Newly diagnosed children without ketoacidosis can be treated with subcutaneous insulin at the dose o.3 to 0.5 u/kg /day. Pubertal children require more amount of insulin 1-1.5u/kg/day . Usually split /mixed regimen is recommended . Insulin regimens using rapidly acting and intermediate acting NPH at breakfast and dinner . 2/3 of total dose in the morning one third in evening. 2/3 of morning dose as NPH and 1/3 rapidly acting analog . The evening dose as ½ NPH and ½ rapid acting analog . Onset of action of NPH insulin begins within 2 hrs and peaks at 5-7hrs lasts for 13 -16 hrs. Action of Rapidly acting insulin such as lispro and aspart starts at 15

minutes peaks at 1-3 hrs and lasts for 3-5 hrs . Short acting insulin should be given to maintain target blood sugar level. Thus achieving glycemic target without hypoglycaemia.

Most common lifethreatening and preventable complication of diabetes is ketoacidosis. Blood sugar >240mg/ with ketonemia/ketonuria, pH <7.3 . As blood sugar >150mg/dl, exceeds renal threshold and causes osmotic diuresis resulting in loss of extracellular water and electrolytes. Accelerated lipolysis which occurs in insulin deficiency leads to conversion of free fatty acids to beta hydroxybutyric acid and acetoacetic acid . Intracellular ion potassium is transported from the cell to plasma in exchange for hydrogen ion lost in urine.

Management of DKA starts with correction of dehydration, electrolyte loss, hyperglycemia and acidosis . Initial fluid therapy is 10-20 ml of 0.9%NS to restore intravascular volume. Maximum < 4 l fluid to be given for 48 hrs to prevent cerebral edema. Rehydration fluid should contain 115 to135meq/l for gradual decrease in serum osmolality and to reduce risk of cerebral edema . Insulin infusion 0 .1u /kg/hr is started . Potassium deficit needs aggressive management with 20-60meq of KCL added to 1L of fluid . To have a gradual fall in blood sugar by 50-100mg/dl/hr continous low dose insulin infusion is administered . Infusion of insulin should be titrated based on blood sugar. Dextrose containing intravenous fluid should be started once blood sugar falls below 300mg/dl . If acidosis persists at lower blood sugar level continue insulin infusion and dextrose . Don’t infuse sodium bicarbonate for correcting acidosis . Stop insulin infusion after correction of acidosis and start on subcutaneous insulin 1 hour before stopping insulin infusion and then start oral. Monitor blood sugar three times.

Insulin Therapy

Currently there are various methods to deliver insulin . These regimens include use of single intermediate or long acting insulin (neutral protamine hagedorn) lente, ultralente or glargine given three or four times a day or aspart /lispro/ regular insulin as subcutaneuous insulin infusion.

Type of diabetes, age, glycemic goals, personal choice and onset,peak and duration of action determines the selection of insulin regimen. There is no estabilised way of measuring insulin requirement in type 1 diabetes. Before developing ketonuria, children are initially started on insulin at low dose of <.5u /kg per day.

In children on steroids, puberty, DKA or infection initial dose may be as high as 1u/kg . Infants and toddlers may require very low dose. Hence for proper dosing, the dose is diluted to 10 u. Diluents are given by manufacturers for each specific type of insulin . Goal of therapy is to maintain premeal blood glucose value of 80-120mg/dl. Dose of insulin is adjusted taking into account the pattern of blood sugar for a period of 3 days .

Usual Subcutaneos Daily Dosage of Insulin in Children and Adolescent S With Diabetes		
TYPE	**NON DKA**	**DKA**
Type 1 diabetes Child,prepubertal	0.25-.5u/kg/day	.5-.75u/kg/day
Adolescent,pubertal	0.5-.75u/kg/day	0.75-1u/kg/day

After few weeks of starting insulin there will be fall in blood sugar level and hence requirement of insulin may decrease, this is due to residual insulin release called as honey moon phase . In type 1 diabetic children due to continued destruction of beta cells, there is increased requirement of insulin over weeks and months of treatment and there may be decline in growth . Inadequate overnight dosing of insulin results in fasting hyperglycemia and ketonuria occasionally . Mixture of rapid and intermediate or long acting insulin are given before meal in the morning and afternoon to maintain blood sugar level. In adolescent there is rise in morning sugar due to afternoon snack . This can be controlled by using aspart or lispro insulin .

Newer insulins are called insulin analogues. They are derived by biochemical alteration of the human insulin . This modification causes alteration in onset, peak and duration of action . Insulin analogues are safe and effective and used for optimal control of blood sugar.

First rapid onset insulin analogue is lispro insulin . Onset of action, peak and duration of action is designed to reduce postprandial blood sugar. So it is ideal to be administered premeal. It’s onset of action is 15 minutes and duration of action 2-4 hrs. It is easy to titrate insulin in erratic eater matching insulin with food intake. Minimises the potential for hypoglycaemia. Lispro can be used in very young children as diluents are available for lispro insulin.

Another rapidly acting insulin approved by FDA is aspart insulin. Similar onset and duration of action is 4-6hrs. It is not approved for children.

Glargine is long acting insulin analogue. Peakless insulin with duration of action being 24 hrs. Mimics the basal insulin produced by beta cells.

It is clear and should be used alone as it is acidic in nature. It is not approved for use in children < 6yrs.

Premixed insulin preparation containing analogues of lispro and intermediate acting insulin is called NPL. It is not used in children as it is not possible to alter the dose of individual insulin.

Action of Various Types of Insulin			
Insulin Type	**Onset**	**Peak**	**Duration**
Insulin aspart	5-10min	1-3hrs	3-5 hrs
Insulin rapid	<15minu	30-90minu	2-4hrs
Regular	30-60min	2-3hrs	3-6 hrs
NPH	2-4hrs	4-10hrs	10-16hrs
Lente	3-4hrs	4-12hrs	12-18 hrs
Glargine	1.1hr	No peak	24 hrs
Ultralente	4-6hrs	8-20hrs	2—24hrs

Insulin Delivery Systems

Most children receive insulin by injection with syringe to provide mixing of insulin and flexibility in dose of short acting and long acting insulin syringe is calibrated to 3/100cc,1/2cc or 1cc and have 29 gauge needle or 30 gauge needle

Insulin pens with disposable needle tips is more advantageous since they offer a discrete, rapid way to administer in children pens are available as disposable devices holding 300u . injections interfere with lifestyle and there is more risk of hypoglycaemia

So use of insulin pumps have better glycaemic control, reduce hypoglycaemia There is a increasing trend in use of pumps in children .insulin pumps provide continuous infusion of insulin over the whole day in an effort to maintain basal insulin production .bolus of insulin is administered at meals or snacks to maintain normal physiological peaks in insulin release in response to food

Advantages and Disadvantages of Insulin Pump Therapy	
Advantages	**Disadvantages**
Greater increased frequency of blood sugar monitoring	More incidence of hyperglycaemia
Intensify the glycaemic control and Few hypoglycaemic episode	DKA due to crumpled infusion
Few injection	Skin abscess
Immediate access to insulin	Change in hypoglycaemic episodes constant attachment to pump

Before discharging diabetic children the caretaker should be educated about method of blood sugar monitoring, and technique of administering subcutaneous insulin. Caretaker should be aware of premonitory symptoms of hypoglycaemia

Monitoring

Self Blood Glucose Monitoring

The patients should perform blood glucose monitoring four to six times a day. This empowers patients and their families. It enhances the understanding of insulin, food, exercise effects on blood glucose. Real time continuous monitoring is expected to be available in future .Target range of 80-120mg /dl at breakfast 80-150mg /dl at other times should be maintained 80% of blood sugar. If pre breakfast blood sugar is high increase the long acting insulin at bed time

Nutritional Management

Nutritional consultation is mandatory in newly diagnosed cases to encourage them to perform 30-60 minutes of exercise for 5 times a week. Calories intake should include 50-55% of carbohydrates, 15 -20% protein 30% fat.

Age Specific Goals

Hb A1c levels must be adjusted to minimise the frequency of hypoglycaemia. Premeal sugar of 100-180mg/dl HbA1C -7.5-8.5 should be maintained in toddlers, school children should maintain at 90-180mg/dl HBA1C -<8% in teenagers blood sugar 80-120mg/dl HbA1C -<7[3]

Psychological Aspects

Evaluation of psychosocial function of child and family is done at diagnosis and periodically. Warning signs that needs evaluation includes declining school performance, recurrent episodes of DKA, new behavioural problems and isolation from friends and activities[1]

Encourage independence and avoid parent & child conflict Hypoglycaemia

One of the limiting factor in implementation of intensive diabetes management is fear of hypoglycaemia. Rapid acting carbohydrate should be given during hypoglycaemia, raise blood sugar by 15-20mg/dl after10 minutes Avoid hypoglycaemia in children as it causes damage to active brain. If blood sugar values are <60mg/dl for 3 times in a week reduce insulin dose

Complications

Complications of type 1 DM includes retinopathy, nephropathy, neuropathy, and cardiovascular disease

Blood glucose control linked with complications so HbA1C should be done at every visit

	WHEN TO COMMENCE SCREENING	FREQUENCY	PREFERRED METHOD OF SCREENING	OTHER SCREENING METHODS
Retinopathy	5 yrs after diagnosis in prepubertal children, pubertal children 2 yrs of diagnosis	1-2 yearly	Fundal examination	Fluorescein angiography, mydriatic ophthalmoscopy
Nephropathy	5 yr afterdiagnosis prepubertal children, after 2 yr in pubertal children	Every year	Overnight timed urine excretion of albumin	24-hr excretion of albumin, urine albumin/creatinine ratio
Neuropathy	Unclear	Unclear	Physical examination	Nerve conduction, thermal and vibration threshold, pupillometry, cardiovascular reflexes
Macrovascular disease	After age 2 yr	Every 5 yr	Lipids	Blood pressure
Thyroid disease	At diagnosis	Every 2-3 yr	TSH	Thyroid peroxidase antibody
Celiac disease	At diagnosis	Every 2-3 yr	Tissue transglutaminase, endomysial antibody	Antigliadin antibodies

Nephropathy

Urine microalbumin is done annually for nephropathy

Urine albumin to creatinine ratio if>30mg rule out orthostatic proteinuria.

Microalbuminuria persists angiotensin converting inhibitors can be used

Lipid Profile

Serum cholesterol and triglycerides are done annually

Maintain LDL at 100MG /dl

Pharmacological treatment is given if LDL ->.160mg

LDL -130-160MG/dl with cardiovascular risk factors

Opthalmogical Evaluation

At diagnosis and annually to rule out retinopathy

Thyroid Disease

Type 1 DM children more prone for other autoimmune disease like hypothyroidism. Thyroid function test is done at diagnosis then annually

Celiac Disease

Anti tissue transglutaminase or antiendomysial antibody at diagnosis

Future prediction, and prevention

There is long prodromic period before overt disease develops. As any other autoimmune disease there is humoral and cellular immune response against multiple target antigens .The markers of prediction includes glutamic acid decarboxylase antibodies, islet cell antibodies and IA2 autoantibodies, insulin autoantibodies and they are detected by immunofloresence and radiolig and assay and ELISA

Type 1 DM is associated with genetic susceptibility gene and the major histocompatability complex. More than 95% of cases were associated with DR3 /DR4. Restriction fragment length polymorphism analysis of DNA from the patients and controls showed stronger association

Inhaled Insulins

Administering insulin via respiratory tract either nasally or into lungs has developed recently. Three randomised control trials were conducted by Cochrane metabolic and endocrine disorders in type 1 patients. Found that there was no significant difference in HbA1C levels on further follow up. There was better glycaemia level in fasting and postprandial sugar and less hypoglycaemic episodes side effects was mild cough

Adjunctive Therapies

Adjunctive therapy were reviewed by Jefferies and colleagues

Categorised into 3 groups

Insulin sensitizing agents-biguanides

Aimed to reduce insulin resistance at puberty

Agents altering gastrointestinal nutrient delivery

Acarbose

Decreases postprandial hyperglycaemia

Pirenzipine

IGF-1

glucagon like peptde

Metformin acts by decreasing hepatic glucose output and improving insulin sensitivity It decreases HbA1c and can be given at a dose of 25-30mg/kg/day. Side effect is gastrointestinal discomfort

Acarbose is a alpha glucosidase inhibitor . It delays absorption of carbohydrate in small intestine and causes 20% reduction in post prandial blood sugar and HbA1c level

Pramlintide (human amylin analog)

Amylin is a 37 aminoacid peptide secreted along with insulin from pancreatic beta cells which regulates gastric emptying and glucose delivery to intestine . It inhibits postprandial nutrient stimulated glucogon secretion . the trial is done in adult which showed reduction in HbA1c and reduction in body weight

Glucogon Like Peptide

It inhibits gasric emptying and stimulates glucose dependent insulin secretion

GAD 65 Antigen Therapy

Alum formulated GAD 65 was tried in children within 3 months of diagnosis. Follow up of these cases was done for 15 months. They found that there was no significant change in clinical outcome.[8]

Prevention

Primary Prevention

Aim is to prevent the disease in high risk population before serological evidence of islet autoimmunity

Cows milk protein is associated with T1 DM and breast feeding has protective effect. So a case control study was done in children with high risk of diabetes and those children who were not given cow milk protein and followed up for 10 yrs. At the end of 4 years none of the children in control group developed overt diabetes

Secondary Prevention

Delay and possibly suppress beta cell damage

European nicotinamide diabetes intervention trial, a double blind placebo trial was done by administering nicotinamide to first degree relatives of T1DM patients with autoantibodies They observed that there was no difference in decrease in beta cell function in both groups. So

concluded that nicotinamide does not stop the decrease in beta cell function

Tertiary Prevention

After onset of disease aimed at inducing prolonged remission

To preserve remaining beta cell function. reliable screening marker of beta cell function is measuring c- peptide

Anti CD3 -OKT3 is under trial

Anti CD20 monoclonal antibody – RITUXIMAB

Pancreas and islet transplantation

Stem cell therapy gene therapy under trial

REVIEW OF LITERATURE

N.Tandon et al conducted a study in north Indian diabetic children to detect prevalence of various autoantibodies. He analysed for GADA, IA-2,ICA-12, 21 OH hydroxylase

Among the101 patients analysed 13.9% were positive for GADA with 14.9% showed positive for IA -2. On using radio binding assay to detect the antibodies prevalence has increased to 26%

Conclusion of this study is that GAD and IA2 antibodies is present in 26% of type 1 DM in north India. MMDM patients have >20% seropositivity for IA2 antibodies ICA-12 IS prevalent in both type 1 DM and MMDM one in every 7 patient shows evidence of coeliac disease[(9)]

Urakami .T etal from Nihon university school of medicine, Tokyo, Japan conducted a study to compare the prevalence of antibodies to GAD and IA--2 at diagnosis in Japanese children

Among the 108 children analysed, 48 Children were mild form of type 1 diabetes and 70 were with early progressive form of type 1 DM, both group of children had prevalence of GADA and IA-2A above 70% . Children with slowly progressive form of type 1DM had low titres .

Titres >100u/ml are frequent in children with RPTID . Antibody titres has no significance in clinical form of disease.

He concluded that mild form of autoimmunity is associated with low titres of antibodies [10]

Lee YS etal from National University of Singapore studied the prevalence of islet cell antibodies (ICA) and GADA in Asian children with DM at diagnosis

The study concluded that among the 41 children analysed 17 of them were positive for ICA and anti –GAD (41.5%). This study also compared children with antibodies to without the antibodies on their age of onset and random c-peptide levels and HbA1c levels and frequency of diabetic ketoacidosis at presentation . There was no significant difference in body mass index, age of onset, c- peptide level, HbA1C,and frequency of DKA

This study concluded that prevalence of autoantibodies in Singapore children (41.5%) is lower than Caucasian population (60%). There is significant proportion of nonimmune mediated type1 DM in Singapore children[11]

Emad Sabbah etal from university of Oulu analysed 747 children with newly diagnosed diabetes for GAD antibodies,IA-2,IAA in relation to clinical characteristics and course of disease in children

Results showed that 73.2% positive for GADA+ 85.7% IA-2A 54.2% for IAA 72.6%for multiple autoantibodies, 2.3% has no detectable autoantibodies. More than one third patient probands tested positive for all autoantibodies 36.9% positive for 3 antibodies 18.9% and 6.3% positivity was seen in for 2 antibodies and 1 antibody respectively. The age of onset in patient positive for GADA is higher than –ve . There was no difference in clinical and metabolic characteristics. c-peptide values(p- .007) are higher in patients with no autoantibodies children positive for IA-CA had low c- peptide levels(p-0.005). multiple antibodies positive patient have low serum c-peptide levels p-<.001 and higher insulin dose . Antibodies negative patients require less exogenous insulin p<.001

He concluded that there is no significant difference in degree of metabolic decompensation between antibody positive and negative patient [(12)]

Francesco Medici etal from St.Bartholomews Hospital London conducted a cross sectional study on antibodies to GAD 65 and tyrosinase phosphatase like molecule in fillipino type 1 diabetic patients

He analysed 91 patients of type 1 DM and 74 type 2 DM and 100 controls 27% showed GAD positive IA2C positive in 8% in type 1 diabetic patients. Type 2 DM had neither of two or controls Among these positive cases 56% of positivity in seen in cases diagnosed within 2 yrs. ICA 2a only in 16%. He compared these results with European patients based on age and disease duration found both of them to be similar.

This study concluded that antibodies to IA 2C is infrequent in filipinos and this being the first study to investigate prevalence and pattern of humoral immune response in type 1 diabetic patient[13]

Claudio Tiberti etal done a study on GAD antibodies and IA-2 autoantibodies in type 1 diabetic patient saliva. Paired serum and saliva were collected and analysed.GAD positive in serum was 64% and in saliva 61% positive

IA -2A positive in serum was 47% and saliva 42%. Detection of antibodies in saliva has high sensitivity and specificity.[14]

Jacob S.Peterson etal had done a study on detection of GAD antibodies in diabetes using radioligand assay in Denmark. He used

invitro transcribed and translated 35S METHIONINE –labelled human islet GAD 65 they concluded that 77% of patients were positive for GAD 65 antibodies [15]

Gary T C Kol etal from Australia conducted a study on antibodies to glutamic acid decarboxylase in young Chinese diabetic patients. He analysed 140 patients based on clinical features, antibodies to GAD and pancreatic beta cell function. They concluded that higher prevalence of GAD positive (29%) in type 1 diabetic patients P-.003 GAD POSITIVE patients have low BMI, early onset of disease, lower blood pressure plasma triglyceride and c-peptide.[16]

David .m Tridgell etal had done a study on interaction of onset and duration of diabetes on the percentage of GAD and IA -2 antibody in diabetic patients. He analysed 5020 individuals and found that antibodies are absent after 5 years of diagnosis . IA-2A positive patients there is no significance between onset and duration of disease. In GAD positive patients there was significance.

He concluded that onset and duration of diabetes have significant effect on antibody status in GAD positive patients [17]

C.B.Sanjeevi et al conducted a study on autoimmunity in Indian diabetics the study concluded that the prevalence of GAD 65 antibodies

in south Indian IDDM patient is 59% and IDDM patient from Cuttack have less prevalence for GAD antibodies. It is more prevalent in female than male which is pronounced in children <12 years .In Belgian patients prevalence of GAD 65 Ab <9years (64%) lower than ICA positive patient. ICA 512 associated with rapid rate of disease progression. Prevalence of ICA and IAA decreases with increasing age of onset prevalence of GAD 65 is unchanged and also included that GAD 65Ab have highest diagnostic significance [18]

Willam .A etal done a study in Swedish children on GAD., islet cell antibodies .He analysed 491 newly diagnosed diabetic children for GAD antibodies .He observed that there is higher sensitivity and specificity for GAD antibodies than ICA and IAA. GAD antibodies are more prevalent in females than in males p<.001.GAD65ab were associated with DQA1 and IAA with DQA1. There is no seasonal variation . Better sensitivity is seen with combining the three antibody. GADA were relatively sensitive/specific for diabetes, [19]

Chao Chen et al had done a study in type 1 DM Chinese patients for GAD and protein tyrosine phosphatise antibody. Among the 247 analysed, majority had persistence of GADA or IA 2A There was a decrease in titre of GADA positive from 56% at onset 50.5% at 1 year 43.3% at 3-5 yrs later. The prevalence of IA -2A were 32.8% 31% and

23.3% at 1 year and 3-5years later the median titres were .0825 at diagnosis

He concluded that for diagnosis of various autoimmune disease repeated analysis of GADA and IA -2A is necessary [20]

Aljabra etal had done a study in the in Saudi Patients with Type diabetes Mellitus on their prevalence of Autoimune antibodies. Among the 171 diabetic patients analysed GADA, ICA and IAA were positive in 53.22% and 76% respectively. With female preponderance GADA, ICA anIAA and those younger than 20 years of age. Children who are positive for GADA had higher levels of ICA and IAA than those negative for GADA. Multiple antibodies (≥2) were more observed in young patients with no gender differences in the prevalence of multiple antibodies . [21]

K. Das[1], A. Shtauvere-Brameus[2] etal conducted a study on The frequency of GAD65 and ICA512 antibodies in Indian IDDM patients is similar to that in Caucasians. The aim was to test whether undernutrition is associated with autoimmunity as evidenced by increased or decreased autoantibody formation in both clinically diagnosed IDDM and NIDDM patients from south India. The prevalence of GAD65 and ICA512 autoantibodies in controls was 4% and 2%, respectively. On analysing 131 patients GAD6 5 autoantibodies were present in 73, and ICA512

antibodies were present in 41 of patients. The result proved that there is no significant difference in prevalence of GAD65 and ICA512 antibody in UNDM patients and NNDM patients. The more prevalence of autoantibodies among NIDDM on comparing with IDDM in both groups suggests high prevalence in slow-onset IDDM. Undernutrition has no predisposition for autoimmunity in south Indian diabetic [22]

Paul Z. Zimmet, etal on the ethnic distribution of antibodies to GAD: and levels in insulin-dependent diabetes mellitus in Europid and Asian subjects. The europids had more prevalence of antibodies to GAD (63%),and was much lower in Asian populations with IDDM: The prevalence amoung Japanese, thai, Korean and Chinese were (31%),(29%), (5%) and 27% respectively. There is no difference in mean level of antibodies to GAD in all groups, The GAD antibodies are more prevalent than islet cell cytoplasmic antibodies. Almost all IDDM patients positive for islet cell antibodies had antibodies to GAD, different autoantibodies are involved in autoimmune process [23]

Sugihara etal conducted a study in Japanese type 1 diabetic patients on clinical significance and course of GAD antibodies over time. Amoung the patients within 6 months of diagnosis of IDDM, 23 were positive. Among the children diagnosed 2 years ago 16 of 49 sera of IDDM patients were positive for GADA .

Controls and NIDDM groups had less prevalence of GADAb than cases of IDDM. Other Autoimmune disease like autoimmune thyroiditis and congenital hypothyroidism, and was more prevalent in recent-onset patients compared to patients with long-standing IDDM. Presence of GAD represents an autoimmune response. GADAb had higher prevalence in females than in males patients. clinical features including residual pancreatic betacell function after diagnosis were demonstrated to be similar betweenGADAb-positive and -negative patients.

In conclusion, by using the radioimmunoassay (RIA) for GADAb revealed a high prevalence of autoimmune reactivity to GAD in Japanese IDDM children. These results, using this RIA procedure, might assist in laying the groundwork for future trials of immunomodulation therapy for IDDM in Japan.[24]

C. Lévy-Marchal, J. Tichet conducted a study on islet cell antibodies in French children Islet-cell antibodies is reported to be of predictive value for the future development of Type 1 (insulin-dependent) diabetes in first degree relatives of diabetic patient. Screening for islet cell antibodies was done in French schoolchildren (6–17 years) by the indirect immunofluorescence technique. Isle. Only 17 sera demonstrated islet-cell antibody titre >-24 JDF units. There was no significant difference between islet-cell antibody-positive and islet-cell antibody-negative children. A second blood sample was collected from 80 of 150 islet-cell antibody positive children after an interval of 8 months. Only 11 sera have titres < 4.5 JDF for islet-cell antibody titres . HLA-DQB typing was performed by restriction mapping techniques in all antibody positive and negative patients. There was no significant difference in distribution of the susceptibility alleles (DQB1-Asp57-negative) between islet-cell antibody-positive and islet-cell antibody-negative children. There is low prevalence rate of islet-cell antibody in French schoolchildren, among whom the incidence rate of Type 1 diabetes is one of the lowest in Europe[25]

Lisa Mansson etal conducted a study on Islet Cell Antibodies represent autoimmune response against several antigens. They selected 30 patient serum samples which is positive for ICA and one other additional autoantibody such as glutamic acid decarboxylase antibodies (GADA), thyrosine phosphatase antibodies (IA-2A) or insulin autoantibodies (IAA). The samples were incubated with the specific antigen (GAD65, IA-2 or insulin) and the ICA analysis and the immunoprecipitation assay were performed before and after the absorption. Specific autoantibodies against GAD65 and IA-2 could be absorbed with the Corresponding antigen, ten GADA positive and six IA

2A positive samples became negative after absorption. Low level of antibodies was persistent the ICA reaction after absorption . This suggest that ICA has immune reaction against not only against beta cells but also other organ specific antigens[(26)]

Kaichi Kida, etal had done a study in Japanese patients on in type 1 diabetic children various autoantibodies like ICA and organ-specific autoantibodies There was a decreasing trend in antibodies titres over years from 73.15 in the first year, and decreased to 58% 18% 2.8% over 5, 10 and above 10 years and has no sex predilection . But the prevalence of other autoantibodies was in increasing trend and more prevalent in female with a significant p- value <.001

In some girls there was a rise in titre of antibodies in parallel to a decrease in insulin secretion prior to onset of overt IDDM which declined thereafter. When asymptomatic autoimmunity is triggered, autoimmunity specific to pancreatic islets is triggered and overt disease sets in presence of other autoantibodies proves Autoimmunity .[27]

Dr. C. F. Verge etal had done a study on detect the presence of Autoimmunity in type 1 dm children on analysing 273 children with the disease to various antibody levels .

Antibodies assay was done by radioimmunoprecipitation, insulin autoantibodies was positive in 176 cases within 4 days of onset of disea se by radioimmunoassay, thyroid antibodies assay was done by ELISA method antigliadin IgA antibodies by enzyme-linked immunoassay, and indirect immunofluroscence was employed to detect anti-endomysial IgA and islet cell antibodies . anti-glutamate decarboxylase was positive in 69%, and 65%,71% 10%, for insulin autoantibodies, islet cell antibodies, anti-thyroid peroxidise . Islet cell antibodies and insulin autoantibodies were positive respectively Absence of antibodies was seen in13.7% and 5.8% were negative for all three antibodies and with more prevalence in females.

There is increase in frequency of antithyroid peroxidase with increasing age. Both anti-glutamate decarboxylase and insulin autoantibodies rises with rise in ICA Asymptamatic celiac disease developed in children with elevations of antigliadin and anti-endomysial antibodies .[28]

Landin-Olsson M etal had done a population based study for prevalence of autoatibodies in newly diagnosed type 1 diabetic children.

Children less than 14 years were analysed to various autoantibodies results showed 84% predominance in positivity for ICA, 43% had insulin autoantibodies; both the antibodies positive in 40% . Islet cell antibodies positive in 3%, insulin autoantibodies in 1% of control group with low positive predictive value of 7% in cases and 4% in control group [29]

T Tuomi, P Björses etal conducted a study on the prevalence of autoantibodies in type 1DM patients with autoimmune polyendocrine syndrome type I. 6 diabetic patients were positive for GAD65 0.9-8.0 yr before the onset of IDDM and in 16 of nondiabetic patients had positive antibodies during a follow-up of 2.4-19.5 yr. Nondiabetic patients had positivity of 28% for GAD6. Fasting C peptide P = 0.003) and first phase ininsulin were lower in patients with than in those without antibodies

In both groups there is no HLA genotype preponderance.

GAD65-Ab-positive nondiabetic patients, but the IDDM high risk genotypes were decreased in frequency among the patients with GAD65-Ab.

He concluded, that nondiabetic autoimmune polyendocrine syndrome type 1patients have positive for GAD65-Ab together with a decreased insulin secretory capacity [30].

Eba H. Hathout, MD etal had done a study on prevalence of Autoimmunity, and HLA Characteristics of Children Diagnosed With Type 1 Diabetes Before . The average age of the study patients enrolled was 2.6 years, body mass index was 16.9 kg/m2, and weight was 106% of average weight for height. On analysing cases with controls body mass index showed no significant difference . More prevalence of positive islet cell antibodies and glutamic acid decarboxylase 65 antibodies These antibodies was significantly less in children with early onset of disease .

There is no significance in frequencies of diabetes-related HLA alleles and haplotypes between the groups. HLA haplotype has negative correlation There was a negative correlation with glutamic acid decarboxylase[31]

H. Barova etal had done a study on AntiGAD positive with type 1 diabetes mellitus and higher prevalence of autoimmune thyroiditis than anti GAD negative patients. His results were anti GAD antibodies was found positive in 35%.female to male ratio was1.4 presence of thyroid antibodies in 24% of type 1 diabetes with GAD POSITIVE compared with GAD negative patients in whom prevalence is 12-4%

He concluded that there is twice prevalence of thyroid antibodies in GAD antibody positive type 1 diabetic patients. Regular examination of thyroid and thyroid function test (thyroid antibodies) is essential in type 1 patients[(32)]

Henrik borg etal conducted a study on presence of GAD antibodies indicates autoimmunity and its assay in children with recently diagnosed diabetes mellitus he studied in 100 children with diabetes and controls in diabetic children GAD antibodies was positive in 66 of 100patients.ICA-was found in 87, IA2-ab in 69% in controls ICA found in 2, IA2abin 1 GADA in 3 patient combining IA2-ab and GADA assays shows more positivity for autoimmunity

He concluded that by radioligand binding assay method to detect IA2-ab and GADA was positive in 69% of newly diagnosed patients

.Though multiple antibodies shows greater frequency, GADA assay is a valuable alternative to ICA assay[33]

Riitta Veijola etal had done a study in HLA dependent genetic susceptibility, autoimmunity and metabolic characteristics in finish type 1 diabetic children with or without affected first degree relatives . He analysed 121 familial cases with 574 non familial cases and found that frequencies of DQB1 is associated high risk of type 1 diabetes mellitus

DQB1 is associated with decreased risk for IDDM was less in familial cases as comparing nonfamilial cases (32.7vs 21.3%,41.3vs 35.9%,18.3vs 31.4%and 7.7 vs 11.4% respectively p-0.002). the frequencies of various autoantibodies in serum namely glutamic acid decarboxylase islet cell antibodies and insulin autoantibodies were similar among familial and nonfamilial cases

31 first affected children were had early onset in familial cases than nonfamilial 90 second affected familial cases had no difference in familial and nonfamilial cases in metabolic decompensation at diagnosis both groups had severe metabolic decompensation . He concluded that as there is no significant difference in autoantibody levels between familial and nonfamilial cases it indicates homogenity than heterogeneity.[34]

Jacob S Peterson etal has done a study on prevalence of islet cell autoantibodies in monozygotic and dizygotic Danish twins with type 1 diabetes mellitus.The results of his study is that prevalence of various autoantibodies against beta cells islet cell antibodies ware 38%, 85%,and 92%respectively in monozygotic twins and 57%,70% and 57% respectively in dizygotic twins Among the children with positive for antibodies the children without diabetes were 20%, 50% and 40% in monozygotic twins and 26%, 49% and 49% in 35 of dizygotic twins

He concluded that the prevalence of ICA in both types of twins were not different, which shows that islet cell autoimmunity is influenced by environmental factors than genetic determination. ICA was more prevalent in nondiabetic twins than in first degree relative s of patients with type 1 diabetes.[35]

Merrill J Rowley etal had done a study on Antibodies to GAD to discriminate Major Types of Diabetes Mellitus. He concluded that The frequency of antibody to GAD in IDDM varies from 69%and 59% among short-duration and in long-duration cases . Islet cell cytoplasmic antibody was positive in patient with disease of longer duration in. Antibodies to GAD were elevated in 5% NIDDM cases and in nondiabetic subjects were negative for antibodies [36]

Eun Gyong Yoo etal had done a study in Korean children on The clinical types and characteristics of Diabetes Mellitus . He analysed 177 diabetic children, grouped as type 1 and 2. All patients with early onset of disease were before the age of 9 years were of type 1, initial serum C-peptide levels were low <0.6(50%), Type 2 had high serum c-peptide >1.5ng/dl. There was a change in types on follow up. Only 55.4% of type 1 DM patients had insulin autoantibody, islet cell cytoplasmic antibody or anti-glutamic acid decarboxylase antibodies..

Results of the study suggest that patients on insulin with positive autoantibody are to be classified as type 1 even if their serum C-peptide levels are within normal range, and the clinical types could change during follow-up.[37]

J Komulaine etal had done a study on presence of autoantibodies andtheir clinical charecteristics in type 1 diabetic children 35 children type 1 diabetic <2years 146 were >of age group2-4.9 years and 620 children of between 5 to14 years the children with early onset of disease had severe metabolic decompensation and low c- peptide levels ICA and IAA were positive in children <2years there is no significant difference in GAD ANTIBODIES in 3 groups . Strong genetic susceptibility was observed in children<5years.[38]

SIMILAR STUDIES IN OUR INSTITUTION

1.Study on prevalence of thyroid dysfunction in type 1

diabetic children

Results -142 diabetic children were enrolled

Among them 23 (16%) of diabetic children had overt hypothyroidism

12(8%) children with diabetes had subclincal hypothyroidism

Among the diabetic children

30(21%) was positive for thyroid peroxidise

21(14%) positive for antithyroglobulin

19(13%) positive for both the antibodies

2. Study on the prevalence of vitamin D levels in type 1 Diabetes Mellitus

Total of 120 children was studied

Mean levels of vitamin D level in the study group was 15.83 ±6.12 where as in control group was 18.43 ±4.66ng/dl

76%of type 1 diabetic children had deficient vitamin levels p value was.02.

AIM AND OBJECTIVES OF THE STUDY

Primary Objective:

To evaluate prevalence of autoimmunity in type 1 diabetes children by detecting GAD antibodies

Secondary Objective:

To compare the insulin requirement and HbA1C in children with GAD antibodies positive and negative new onset diabetic children

STUDY JUSTIFICATION

- Wide variation in prevalence of positive for GAD antibodies in various population

- Less number of studies in South Indian population

MATERIAL AND METHODS

Methodology

Study Place	Institute of Child Health and Hospital for Children, Egmore, Diabetic Clinic
Study Design	Descriptive
Study Place Setting	Diabetic op in ICH
Study Period Duration	1 year (August 2013 to August 2014)

Case Definition

According to ISPAD guidelines 2011

Criteria for diagnosis of diabetes

Symptoms of diabetes plus random blood glucose concentration more than 11.1mmol/l (200mg/dl)

or fasting plasma glucose>7mmol/l >126mg/dl or

2 hour postload glucose >11.1mmol/l (200mg/dl) during OGTT or HbA1c >6.5

Study Population

Inclusion criteria-children with newly diagnosed diabetes between age 1 to 12years

Exclusion criteria- syndromic children

Sample size- 50 children within one year of presentation

Ethics

Institution review board clearance was obtained

Written informed consent was obtained from the parents of diabetic children

Manoeure

This is a descriptive study conducted in Institute of Child Health in Egmore, Chennai. We included the diabetic children between the age of 1-12years who are attending diabetic clinic. After getting informed consent from parents children were included in this study

Diagnosis of type 1 diabetes milletus based on ISPAD Guidelines

Symptoms plus RBS >200mg/dl

Fasting blood sugar->126mg/dl

2 hours post prandial glucose >200mg/dl during oral glucose tolerance test

After conforming the diagnosis and written consent

Demographic variables like name, age, sex,

Family history of diabetes present or not are recorded, and

Physical examination done.

Whether the child presented as a case of DKA or NDKA if DKA first episode or not

In case of DKA history recording

polyuria

polydypsia,

polyphagia,

vomiting abdominal pain

Breathlessness present or not were noted

In case of NDKA whether the patients are symptomatic or not noted

Anthropometry including

Height,

Weight,

BMI and Recorded.

BP is recorded.

Presence of vitiligo, acanthosis nigricans,

Thyroid swelling present of not

After explaining the procedure 2ml of venous blood was taken from cases and presence of GAD autoantibodies in serum was tested by ELISA method HbA1c, thyroid profile. serum cholesterol were obtained from records

Age was categorised into 4 groups children between 1-3 yrs,4-6yrs, 7-10yrs, >10yrs

Sex categorised as male and female.

Family history categorised as positive and family history negative.

Positivity for GAD antibodies was analysed titre more than 10 iunits considered as GADA positive -1.

GADA negative – titre less than 10 iunits

Hb A1c measured value is categorised into values <8 as good control and >8 as poor control.

Requirement of insulin is categorised based on body weight as requirement less than 1u/lkg or more than 1 unit per kgThyroid status is categorised as normothyroid or hypothyroid.

After calculating the percentage 95% confidence interval is calculated using this formula

$p \pm 1.96 * \sqrt{p(1-p)/n}$

p=0.42

n=50

on applying this formula 95% confidence interval is calculated

STATISTICAL ANALYSIS

The datas were entered in excel sheet

- Proportion will be calculated
- Comparison of study parameters with patient

  Who are positive for GAD antibodies and negative

Statistical analysis of data will be performed by statistical software SPSS

RESULTS

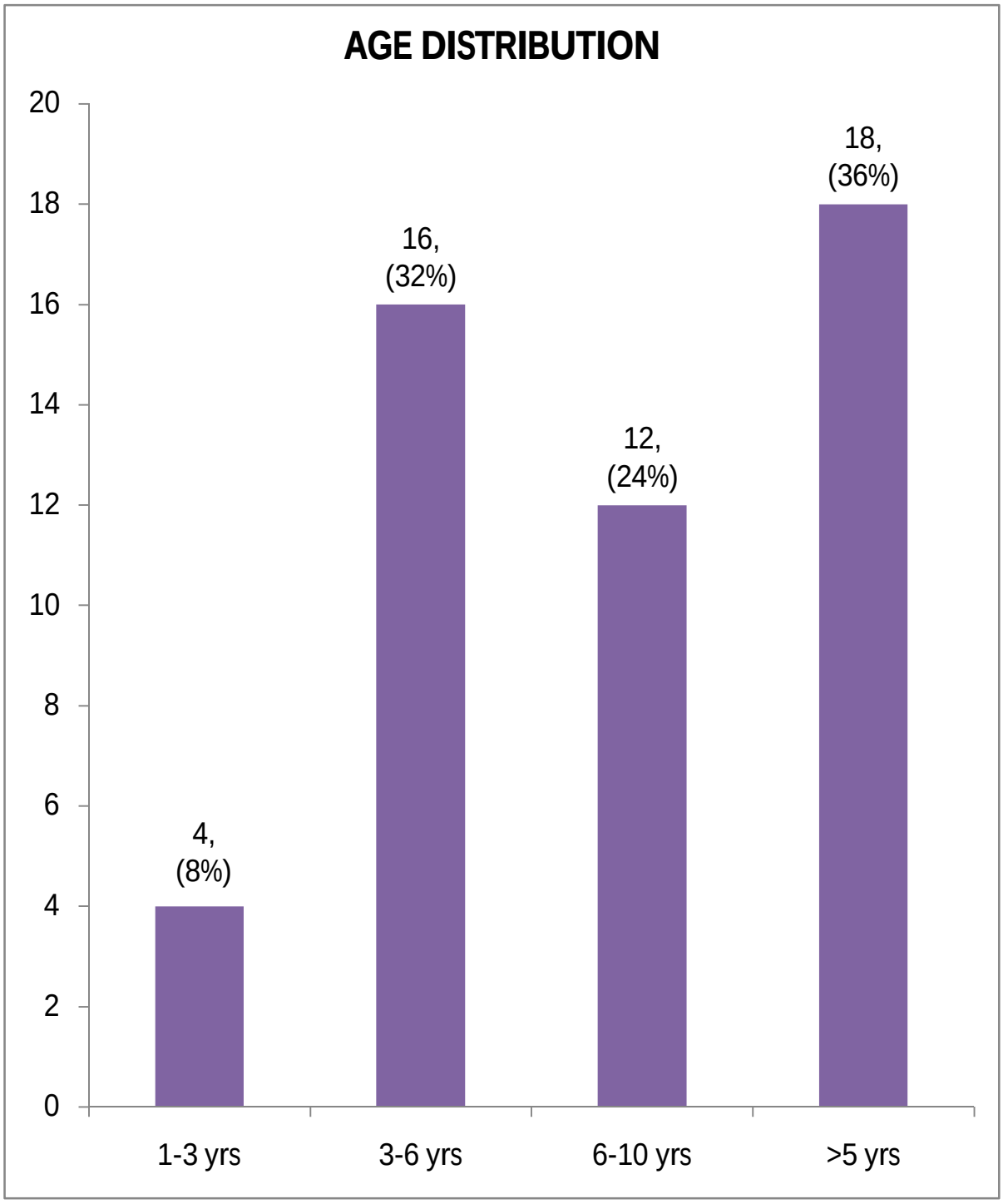
50 children with newly diagnosed diabetes mellitus attending diabetic clinic were analysed for presence of GAD antibodies.

The following were the characteristics of study population

AGE DISTRIBUTION

Age	Number	Percentage
1-3yrs	4	8
4-7yrs	16	32
8-10yrs	12	24
>10yrs	18	36
Total	**50**	**100**

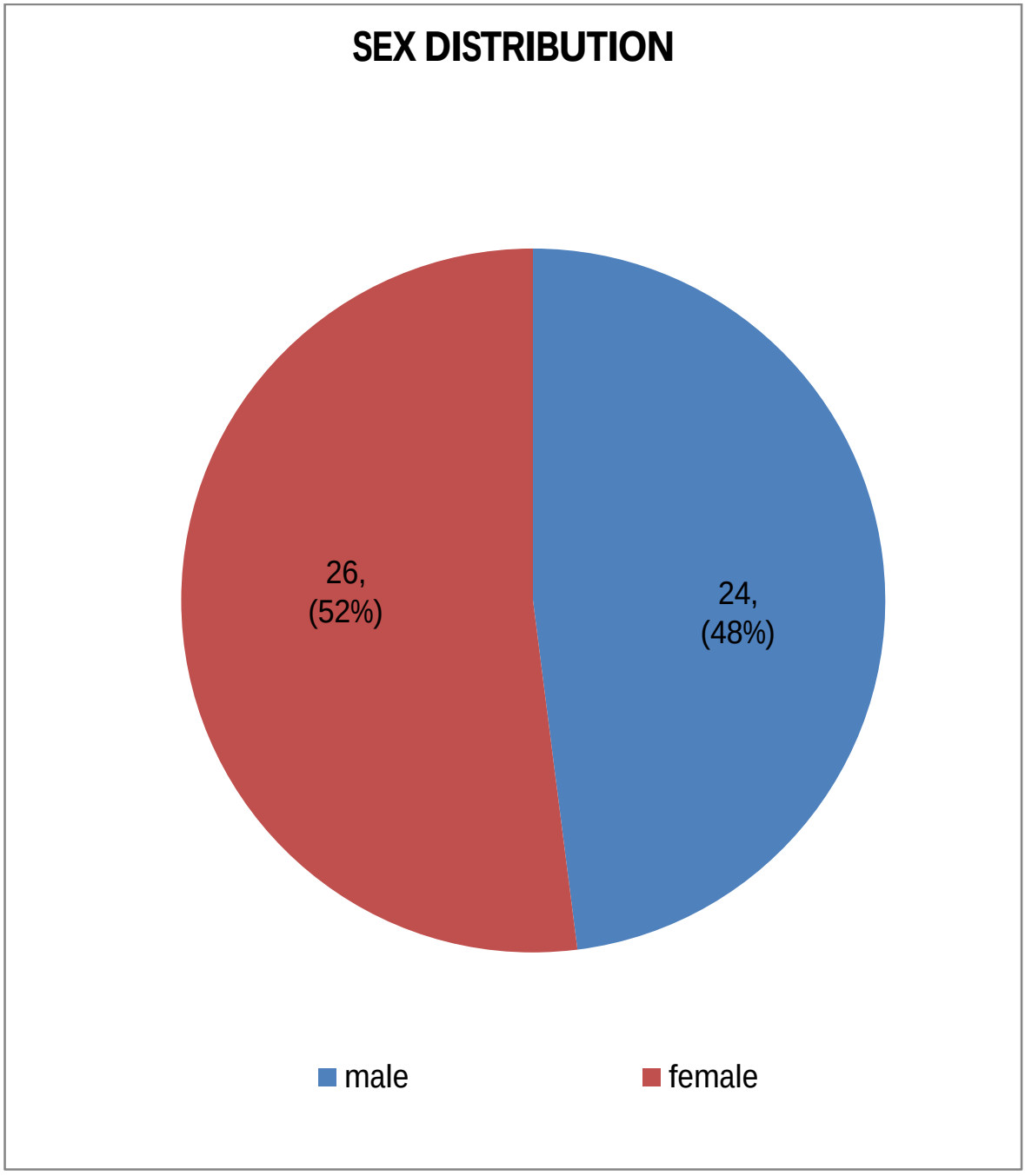
- On analysing the 50 children with diabetes 4 children were between 1-3 yrs and 16 children between 4-7 yrs, 12 children between8-10yrs and 18 belong to age group more than 10yrs


AGE DISTRIBUTION
20
18
16
14
12
10
8
6
4
2
0
4, (8%)
16, (32%)
12, (24%)
18, (36%)
1-3 yrs
3-6 yrs
6-10 yrs
>5 yrs

SEX DISTRIBUTION

Sex	Number	Percentage
Male	24	48
Female	26	52
Total	**50**	**100**

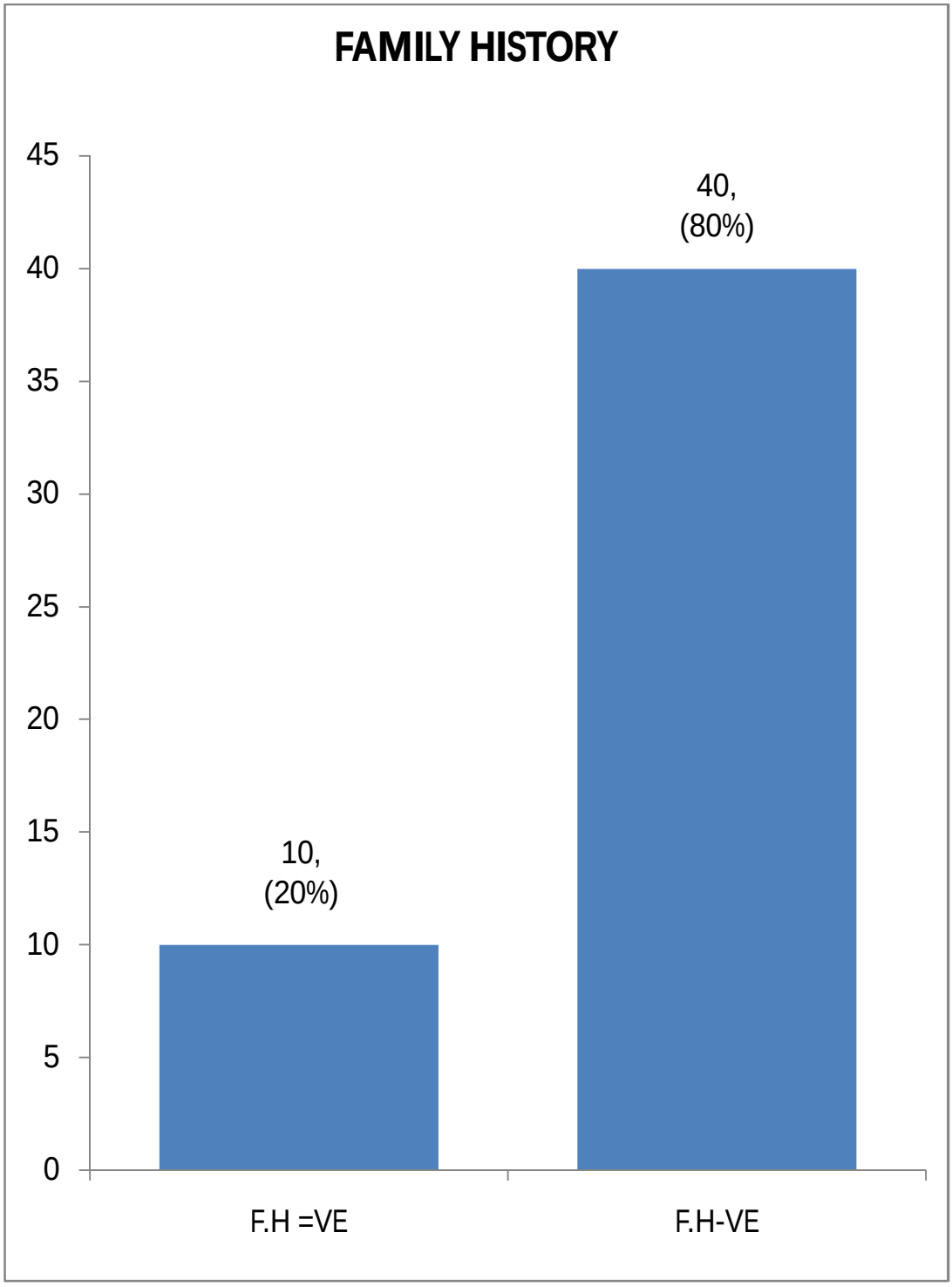
- On analysing the gender distribution 24 of them were male and 26 of them were female shows near equal distribution
- Sex ratio 1:1.1


SEX DISTRIBUTION
26,
(52%)
24,
(48%)
male
female

FAMILY HISTORY

Family history	Number	Percentage
Present	**10**	**20**
Absent	**40**	**80**
Total	**50**	**100**

- On analysis based on their family history only **10** among of them had **positive family history** and **40** of them **had negative family history**

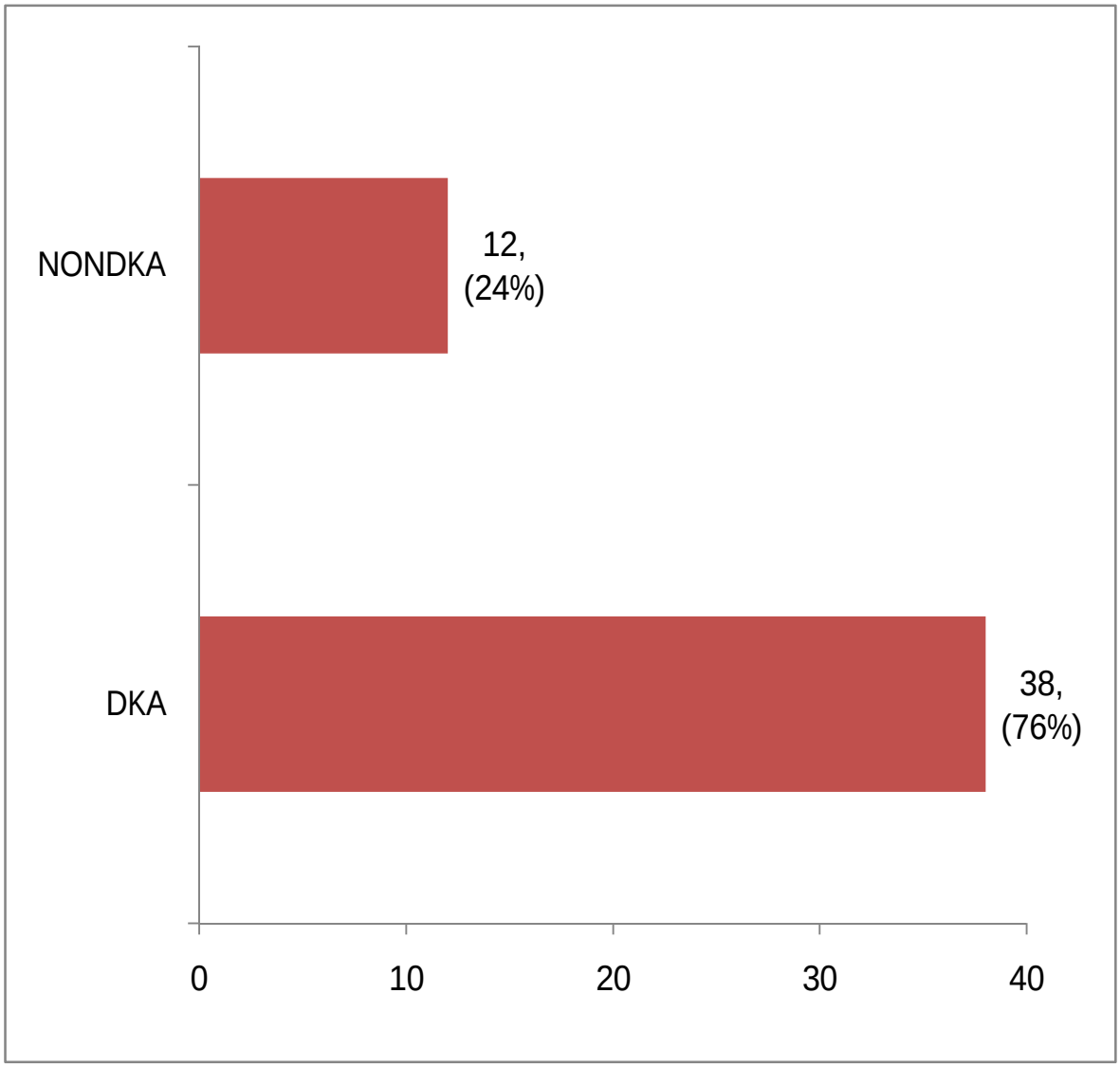

FAMILY HISTORY
45
40
35
30
25
20
15
10
5
0
40,
(80%)
10,
(20%)
F.H =VE
F.H-VE

INITIAL PRESENTATION

Initial Presentation	Number	Percentage
DKA	38	76
NONDKA	12	24
TOTAL	**50**	**100**

- More than **75% of them presented with diabetic ketoacidosis and only 24 % presented as non diabetic ketoacidosis**

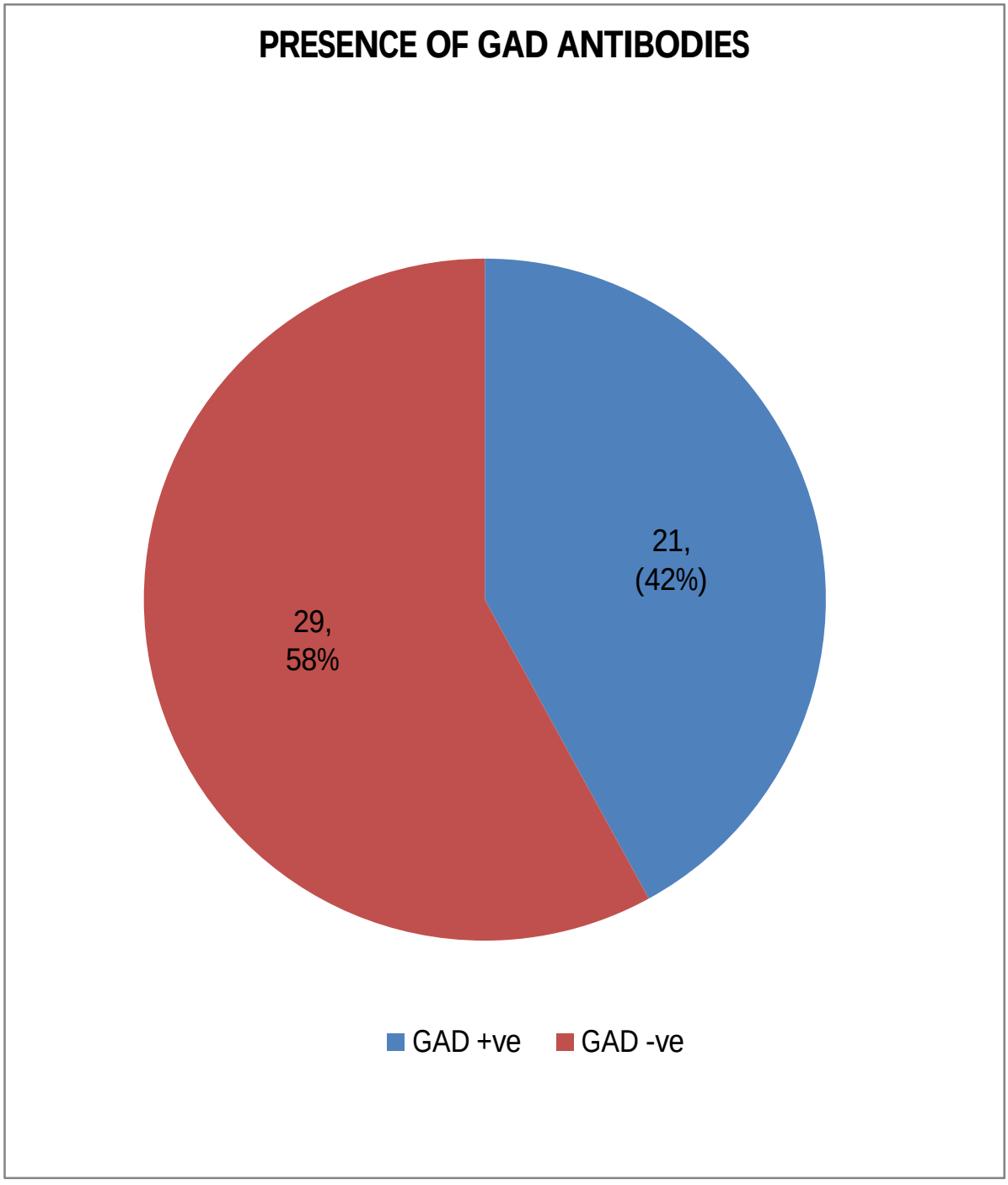
INITIAL PRESENTATION



PRESENCE OF GAD ANTIBODIES

GAD antibodies	Number	Percentage
Positive	21	42
Negative	29	58
	50	**100**

- The prevalence of GAD antibodies in our study **was 42% with 95% confidence interval of 56 -28.**

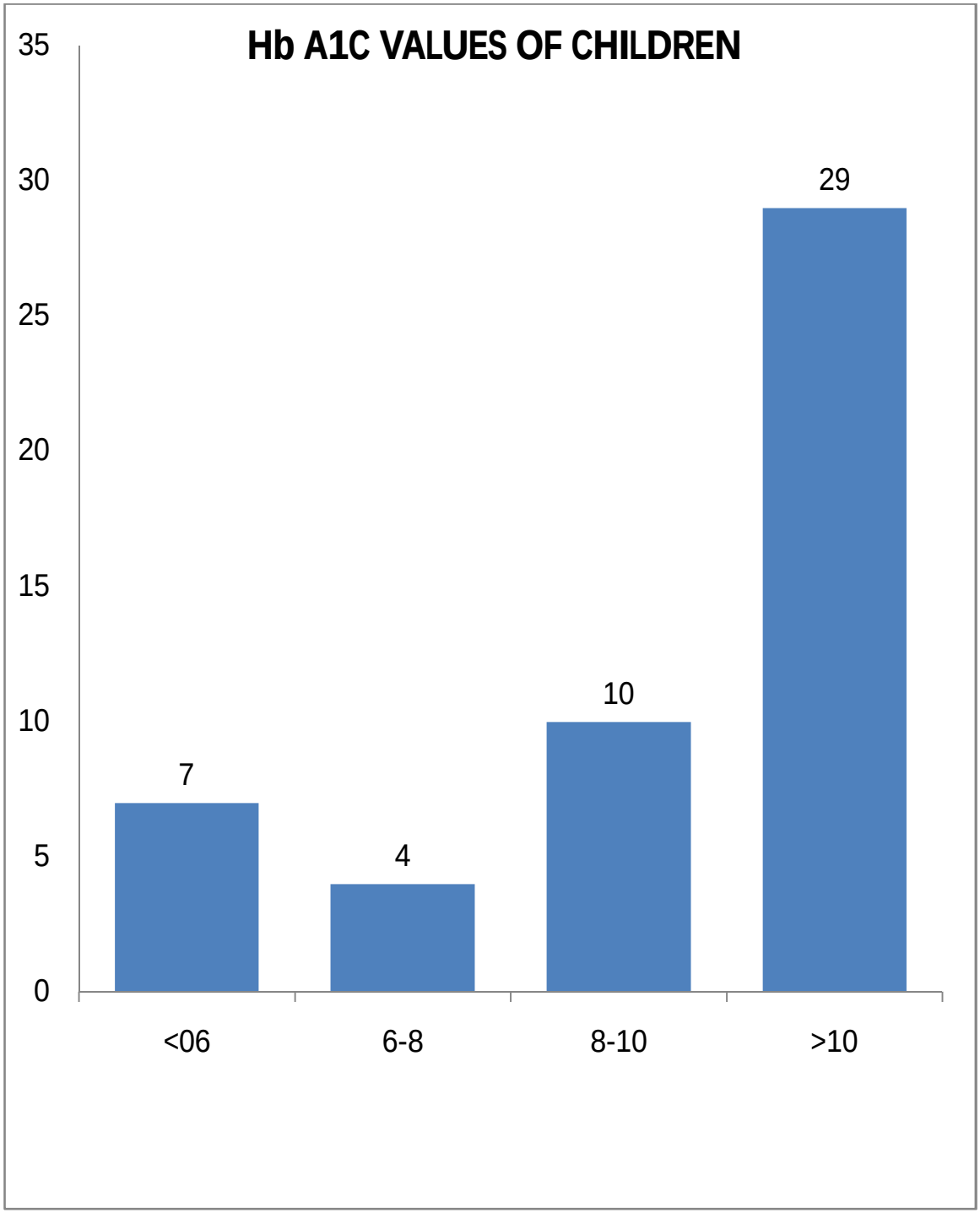


- Among the 50 patients analysed **21 were GAD positive** and 29 were GAD negative

Hb A1C VALUES OF CHILDREN

HbA1C values	Number
<6	**7**
6-8	**4**
8-10	**10**
>10	**29**

- Majority of children had **high HbA1 C (>10)**

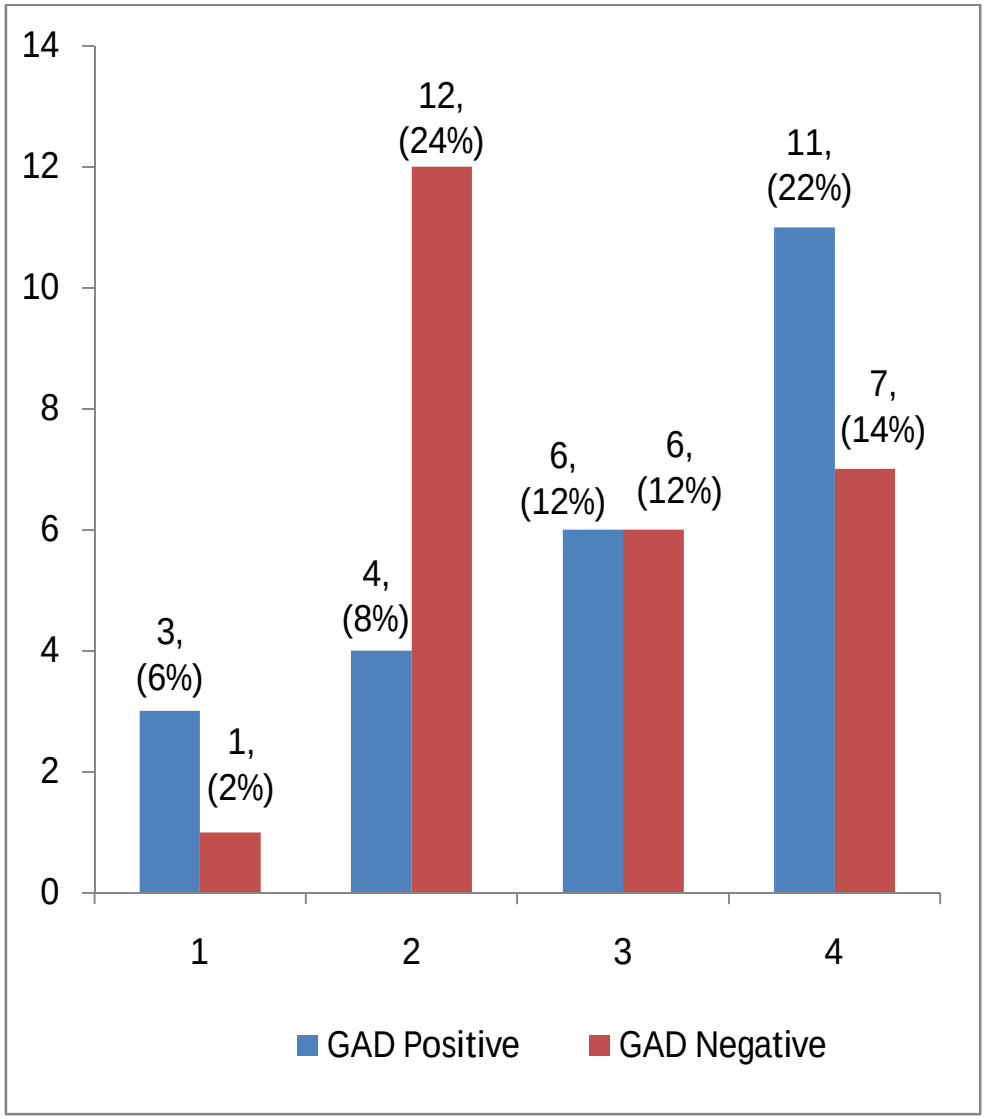

Hb A1C VALUES OF CHILDREN
35
30
25
20
15
10
5
0
7
4
10
29
<06
6-8
8-10
>10

COMPARISON OF GAD POSITIVE WITH AGE DISTRIBUTION

Age Interval	Gad Antibodies		Total
	Positive	**Negative**	
1-3yrs	3	1	4
4-6yrs	4	12	16
7-10yrs	6	6	12
>10yrs	11	7	18
	24	**26**	**50**

- On analysing the age distribution with GAD antibodies, among the children with **positive for GAD antibodies18 children were more than 10 years**

COMPARISON OF AGE DISTRIBUTION WITH PRESENCE OF GAD ANTIBODIES



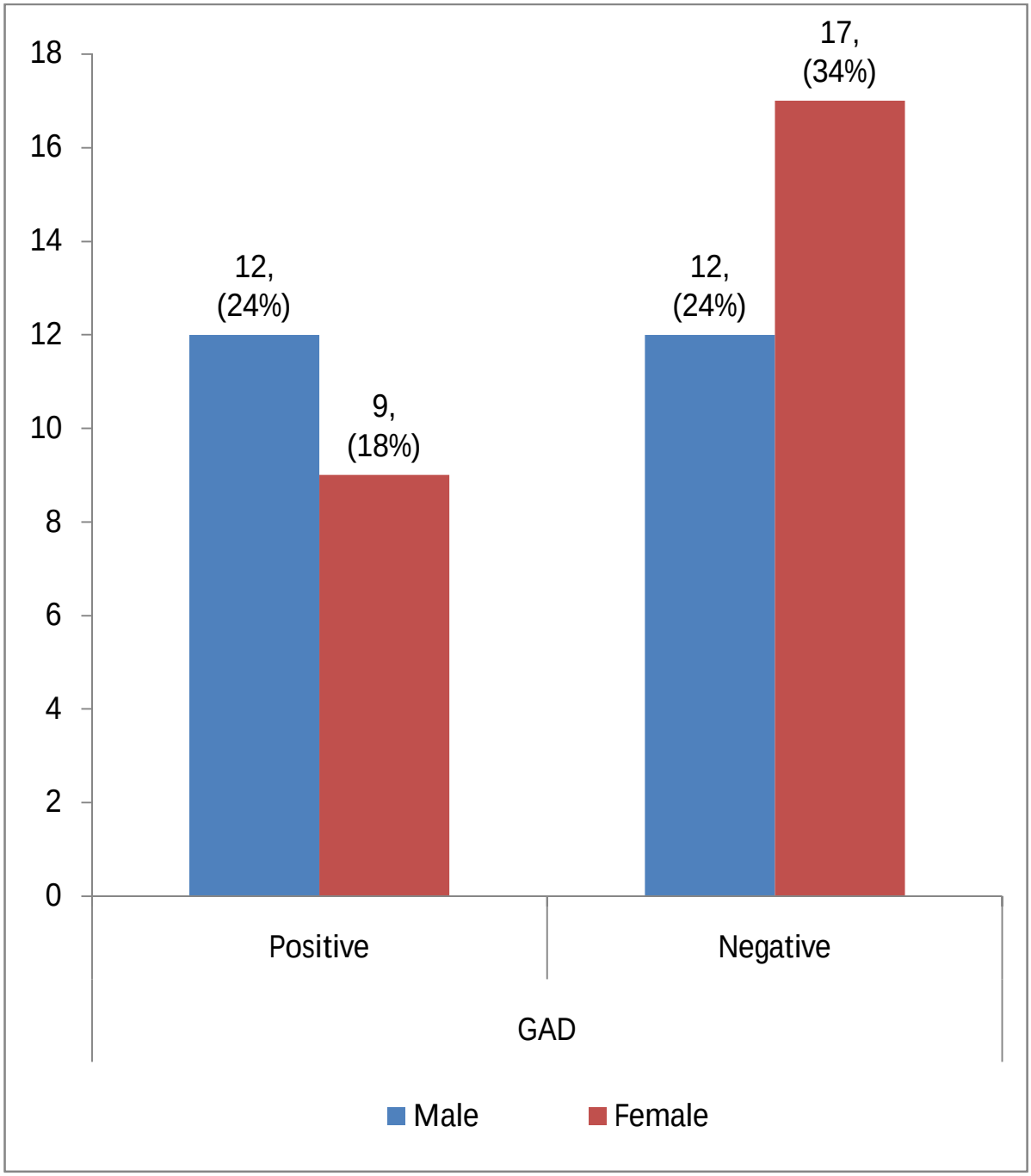
- Children **above 10 Years have higher prevalence**

COMPARISON OF SEX DISTRIBUTION WITH GAD ANTIBODIES

Sex	GAD ANTIBODIES		Total
	Positive	**Negative**	
Male	12	12	24
Female	9	17	26
	21	**29**	**50**

- On comparing sex distribution with presence of **GAD antibodies positive** cases are more prevalent in male children

COMPARISON OF SEX DISTRIBUTION WITH GAD ANTIBODIES

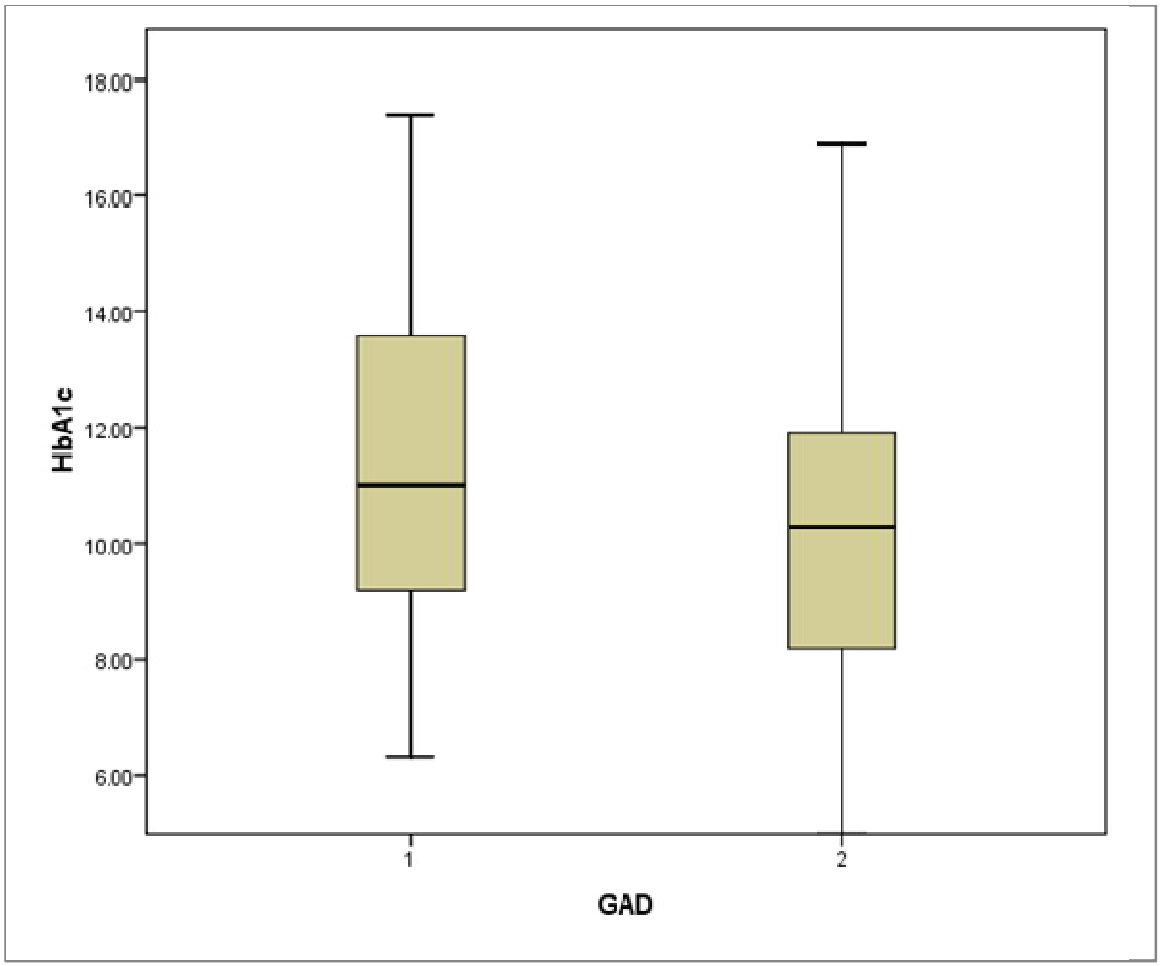


COMPARISON OF GAD ANTIBODIES WITH HbA1C

HbA1C	GAD+ve	GAD-VE	TOTAL
<8	4(36%)	7(63.6%)	11
>8	17(43.6%)	22(56.4%)	39
TOTAL	**21**	**29**	**50**

- On calculating p- value using chi –square
- P value -0.184 (>0.05)
- So not significant

COMPARISON OF GAD POSITIVE WITH HbA1C



- The **median** value of HbA1c in GAD positive patients **was11.0** and **interquartile was 5.15**

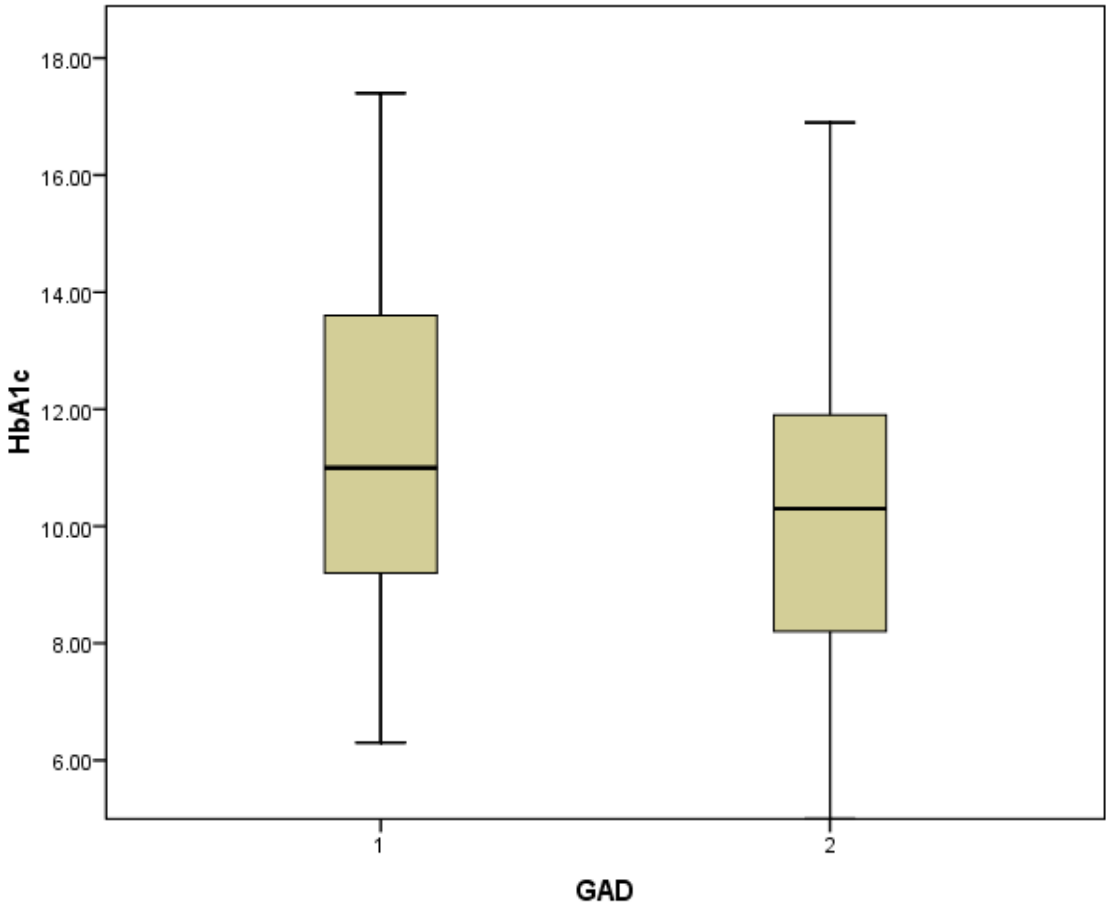
- The **median** value of HbA1c in GAD negative patients was **10.3** and **interquartile** was **4.35**

COMPARISON OF INSULIN REQUIREMENT WITH POSITIVE FOR GAD ANTIBODIES

Insulin requirement	**GAD +ve**	**GAD -ve**	
<1unit	**7**	**7**	14
>1unit	**14**	22	36
total	21	29	50

- Calculating p value by chi square test
- P value-0.31(>0.05)
- So p value is insignificant

COMPARING INSULIN REQUIREMENT WITH GAD ANTIBODIES



- On comparing insulin requirement with GAD,in children with GAD POSITIVE median value was1.3 and interquartile was90
- In GAD NEGATIVE median value was 1.45 and interquartile was 80

DISCUSSION

In our study we analysed 50 newly diagnosed type 1 diabetic children attending our diabetic clinic.

On analysing prevalence of GAD antibodies

- In our population the prevalence was 42%
- Prevalence of type 1 diabetes was high in children above10 years of age.
- There is no significance in family history.
- HbA1c values were high at presentation
- Even though there is clinical significance in insulin requirement in GAD positive and negative patient statistically there is no significance in insulin requirement
- There were only 2 children with thyroid swelling.
- One among them had low T3 and TSH and thyroid antibodies positive

On comparing our study with a study done by Lee etal from Singapore children for prevalence of GAD antibodies the results are similar to our study 41 % had GAD antibodies positive but age of onset

was 7yrs but our study concluded that peak age of onset was > 10 years and high HbA1c

- Similar studies done in finland children on prevalence of antibodies in diabetic children.
- The results were 73.2% were GAD positive 85% for IA2A 54%IAA younger children were positive for multiple antibodies $p<0.001$
- The prevalence is high compared to our study
- There was no significant difference in metabolic decompensation at diagnosis in children with GAD positive and negative patients

Another study done among finland children showed

- 73% had GAD antibodies positive and 85,7% for IA -2A 54.2% for IAA
- on comparing with our study the prevalence rate is high
- There is no significant in degree of metabolic decompensation at diagnosis which is similar to our study
- Antibodies negative individuals have low insulin reqirement compared to positive individuals

- An author named Francesco had done a similar study in Filipino type 1 diabetic patients
    - He analysed 91 patients by cross sectional study
    - 27% were positive for GAD antibodies within 2 years of diagnosis
    - In recently diagnosed patients positivity has raised to 56%
    - on comparing with our study the prevalence is high

A study done in Chinese patients

- The prevalence of GAD antibodies in insulin deficient patients is 29%

  On comparing with our study the prevalence of GAD antibodies is low

Similar study in north Indian population showed that

- Prevalence of GAD antibodies and IA 2 was 26%
- Prevalence is less compared to our study

William a. Hagoplan has done a study in Swedish children s

- The sensitivity and specificity was70 /96 % for GAD antibodies

  84/96% for ICA, for IAA 93/93%
- Compared to our study there is high prevalence in Swedish children

An author A.K.Das had done a study on gad65 and ICA512 antibodies in undernourished and normally nourished south Indian patients he concluded that patients with onset <5years duration was 55% which is higher than in our study

COMPARISON OF GAD ANTIBODIES IN VARIOUS STUDIES

Lee et al	40%
N.Tandon et al	26%
Urkami et al	70.8%
Emad sabbah et al	73.2%
Francesco et al	27.4%
Gary et al	12.1%
William A hagoplan	96%
Chao chen et al	56.3%
Henrik borg et al	38%, 57% in mono and dizygotic twins

This is a prime study done in a tertiary care center in south Indian children with diabetes. Considering that the disease is rare in children sample size is limited .

Presence of GAD autoantibodies implies autoimmune etiology of the disease

CONCLUSION

GAD antibodies was present in about 42% of South Indian type 1 diabetes mellitus

There is no correlation with metabolic derangement and presence of GAD antibodies

LIMITATIONS

- Limited Sample size
- Only a single antibody assay was done

RECOMMENDATIONS

- Larger sample size can be achieved by multicentric study

- Other antibodies like IAA, ICA, anti thyroid antibodies autoantibodies level can be analysed

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ABBREVATIONS

DM – Diabetes Mellitus

GAD – Glutamic Acid Decarboxylase

IAA – Insulin Associated Antibodies

ICA - Islet Cell Antibodies

DKA- Diabetic ketoacidosis

NDKA- Non Diabetic Ketoacidosis

IDDM- Insulin Dependent Diabetes Mellitus

NIDDM- Non Insulin Dependent Diabetes Mellitus

MHC- Major Histo compatibility

PROFORMA

NAME : ADDRESS :

AGE :

1-3 Yrs	3-6 Yrs	6-10Yrs	above 10Yrs

SEX :

M	F
1	2

HISTORY

1. AGE OF ONSET :

1-3 Yrs	3-6 Yrs	6-10 Yrs	above 10Yrs

2. FAMILY HISTORY :

Y	N
1	2

IF YES

PARENTS	SIBLINGS

3. EDUCATION OF PARENTS

MOTHER	FATHER

4. SOCIO ECONOMIC STATUS

(a) ANNUAL INCOME

5. DURATION OF DIABETES AT TIME OF SAMPLING FOR GAD ANTIBODIES

CLINICAL FEATURES

1. INITIAL PRESENTATION

DKA	NON DKA
1	2

(a) IF DKA

KNOWN DIABETIC	FIRST EPISODE
1	2

(b) KNOWN DIABETIC

NO. OF EPISODES
1

© PRECIPITATING FACTORS

INFECTION	POOR COMPLIANCE	BOTH
1	2	3

NON DKA

INCIDENTAL	SYMPTOMATIC
1	2

SYMPTOMS	1 (Y)	2(N)
POLYURIA		
POLYDOPSIA		
VOMITING		
ABD. PAIN		
WT. LOSS		

EXAMINATION :-

ANTHROPOMETRY : Ht. →
: Wt. →
: BMI →

	Y	N
VITILIGO		
ACANTHOSIS NIGRICANS		
HYPERTENSION B.P		

THYROID SWELLING :

Y	N

INVESTIGATION :-

1. BLD GLUCOSE LEVEL AT PRESENTATION →
2. HB A1C LEVEL →
3. THYROID PROFILE →

NORMO THYROID	HYPO THYROID
1	2

4. GAD ANTIBODIES →

POSITIVE	NEGATIVE
1	2

5. "C" PEPTIDE LEVEL →
6. Sr. INSULIN LEVEL →

INSULIN REQUIREMENT AT PRESENT →

13. I have understand that my child's identity will be kept confidential if my child's data are publicly presented

14. I have had my questions answered to my satisfaction.

15. I have decided my child can beparticipated in the research study.

I am aware that if I have any question during this study, I should contact the investigator. By signing this consent form I attest that the information given in this document has been clearly explained to me and understood by me, I will be given a copy of this consent document.

Name and signature / thumb impression of the parents/guardian

Name _____ Signature_____ Date_____

Name and Signature of impartial witness:

Name _____ Signature_____ Date_____

Name and Signature of the investigator or his representative obtaining consent:

Name _____ Signature_____ Date_____

13. I have understand that my child's identity will be kept confidential if my child's data are publicly presented

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Name _____ Signature_____ Date_____

Name and Signature of the investigator or his representative obtaining consent:

Name _____ Signature_____ Date_____

ஒப்புதல் படிவம்

ஆராய்ச்சி நடத்தப்படும் இடம் : **சர்க்கரை நோய் பிரிவு அரசு குழந்தைகள் நல மருத்துவமனை மற்றும் ஆராய்ச்சி நிலையம், எழும்பூர், சென்னை - 600008.**

ஆராய்ச்சியாளரின் பெயர் : மருதாகலஷ்மி.ரா
பட்ட மேற்படிப்பு மாணவர், குழந்தைகள் நல பிரிவு, அரசு குழந்தைகள் நல மருத்துவமனை மற்றும் ஆராய்ச்சி நிலையம், சென்னை-8.

பங்கேற்பாளரின் பெயரின் : வயது: பாலினம் :

மருத்துவமனை எண் :

1. எனக்கு இந்த ஆராய்ச்சி குறித்து முழுவதுமாகவும், விரிவாகவும் எடுத்துரைக்கப்பட்டது.
2. எனக்கு இந்த ஆராய்ச்சியில் இருக்கும் உரிமை மற்றும் பங்கேற்பும் எடுத்துரைக்கப்பட்டது.
3. நான் என் முழுமனதுடன் என் குழந்தை இந்த ஆராய்ச்சியில் பங்கேற்க சம்மதிக்கிறேன்.
4. எனது குழந்தை ஆராய்ச்சியாளருக்கு இறுதிவரை ஒத்துழைப்பு வழங்கும் என உறுதி அளிக்கின்றேன்.
5. எனக்கு எனது குழந்தைக்கு இந்த ஆராய்ச்சியனால் ஏற்படும் நன்மைகள் மற்றும் தீமைகள் பற்றி நன்றாக எடுத்துரைக்கப்பட்டது.
6. எனது குழந்தை இதற்கு முன் வேறு ஆராய்ச்சியில் பங்கேற்கவில்லை என்று உறுதி அளிக்கிறேன்.
7. நான் எப்பொழுது வேண்டுமானாலும் எனது குழந்தையை இந்த ஆராய்ச்சியில் இருந்து விலக்கிக் கொள்ளாம் என்று எனக்கு எடுத்துரைக்கப்பட்டது.
8. என் குழந்தையிடம் இருந்து பெறப்படும் விவரங்களும் எனது குழந்தையின் தன்னடையாளங்களும் வேறு யாருக்கும் தெரிவிக்கப்படமாட்டாது என எனக்கு உறுதி அளிக்கப்பட்டது.
9. எனக்கு ஏதேனும் இந்த ஆராய்ச்சி குறித்து சந்தேகம் இருப்பின் அதனை உடனே ஆராய்ச்சியாளரிடம் கேட்டு தெளிவு பெற்றுக் கொள்வேன் என்று உறுதி அளிக்கிறேன்.

ஆராய்ச்சியாளரின் கையொப்பம்

பங்கு பெறும் குழந்தையின் பெற்றோர் / பாதுகாவரின் கையொப்பம்

நான்:

ஆராய்ச்சியில் பங்கு பெறுவோர்க்கான தகவல் படிவம்

ஆராய்ச்சி நடத்தப்படும் இடம் : சர்க்கரை நோய் பிரிவு அரசு குழந்தைகள் நல மருத்துவமனை மற்றும் ஆராய்ச்சி நிலையம், எழும்பூர், சென்னை-600008.

ஆராய்ச்சியாளரின் பெயர் : மரு.நாகலஷ்மி.ரா
பட்ட மேற்படிப்பு மாணவர், குழந்தைகள் நல பிரிவு, அரசு குழந்தைகள் நல மருத்துவமனை மற்றும் ஆராய்ச்சி நிலையம், சென்னை-8.

பங்கேற்பாளரின் பெயரின் மருத்துவமனை எண் : : வயது: பாலினம் :

ஆய்வின் தலைப்பு : வகை ஒன்று நீரிழிவு நோயினால் பாதிக்கப்பட்ட சமீபத்தில் நோய் அறியப்பட்ட குழந்தைகளின் உள்ளார்ந்த நோய் எதிர்ப்புச் சக்தியின் பங்களிப்பு மற்றும் சர்க்கரை நோயை கட்டுப்படுத்துதல் ஆகியவற்றின் இடையிலான தொடர்பினை மதிப்பீடு செய்தல்.

1. நாங்கள் உங்கள் குழந்தையை இந்த ஆய்வில் சேர்க்குமாறு கேட்டுக் கொள்கிறோம்.
2. நாங்கள் உங்கள் குழந்தை எங்கள் பிரிவுக்கு வந்து சேர்ந்தவுடன் சில மருத்துவ கணக்கீடுகள் பதிவு செய்யப்படும் பின்பு குழந்தையின் ரத்தம் பரிசோதனை செய்யப்படும்.
3. இப்பரிசோதனை செய்ய நேரம் அதிகபட்சமாக 15 நிமிடங்களுக்கு மேல் எடுத்துக் கொள்ளப்படமாட்டாது.
4. தங்களின் குழந்தையிடம் இருந்து பெறப்படும் தகவல்கள் மருத்துவ கணக்கீடுகள் வேறு யாரிடம் தெரிவிக்கப்படமாட்டாது. அவர்களின் தன்னடையாளங்கள் ஆராய்ச்சியின் முடிவில் வெளியிடப்படமாட்டாது.
5. இந்த ஆய்வில் பங்கு பெறுவது உங்களது சொந்த விருப்பமே. நாங்கள் எப்போது வேண்டுமானாலும் இவ்வாராய்ச்சிலிருந்து விலகிக் கொள்ளலாம். நாங்கள் விலகிக் கொள்வதால் தங்கள் குழந்தைக்கு அளிக்கப்படும் சிகிச்சையில் எந்தவித மாற்றமும் இருக்காது.
6. ஏதேனும் புதிய கண்டுபிடிப்புகள் / தகவல்கள் அறியப்பட்டால் அது தங்களுக்குத் தெரிவிக்கப்படும்.

ஆராய்ச்சியாளரின் கையொப்பம் பங்கு பெறும் குழந்தையின் பெற்றோர் / பாதுகாவலரின் கையொப்பம்

நான்

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI-3

EC Reg No.ECR/270/Inst./TN/2013
Telephone No : 044 25305301
Fax : 044 25363970

CERTIFICATE OF APPROVAL

To
Dr. R. Nagalekshmi,
Postgraduate
Department of Pacdiatrics,
Institute of Child Health & HC,
Madras Medical College, Chennai-3.

Dear Dr. R. Nagalekshmi,

The Institutional Ethics Committee of Madras Medical College, reviewed and discussed your application for approval of the proposal entitled **"To evaluate role of autoimmunity in recently diagnosed type-I diabetic children attending the diabetic clinic and its relation with diabetic control"** No.06062014

The following members of Ethics Committee were present in the meeting held on 03.06.2014 conducted at Madras Medical College, Chennai-3.

1.	Dr. C. Rajendran, M.D.	-- Chairperson
2.	Dr. R. Vimala, M.D., Dean, MMC, Ch-3.	-- Deputy Chair Person
3.	Prof. Kalaiselvi, MD., Vice-Principal, MMC, Ch-3	-- Member
4.	Prof. Nandhini, M.D. Inst. of Pharmacology, MMC, Ch-3.	-- Member
5.	Dr. G. Muralidharan, Director Incharge , Inst. of Surgery	-- Member
6.	Prof. Md Ali, MD., DM., Prof & HOD of MGE, MMC, Ch-3.	-- Member
7.	Prof. Ramadevi, Director i/c, Biochemistry, MMC,Ch-3.	-- Member
8.	Prof. Saraswathy, MD., Director, Pathology, MMC, Ch-3.	-- Member
9.	Prof. Tito, Director, i/c. Inst. of Internal Medicine, MMC	-- Member
10.	Thiru. Rameshkumar, Administrative Officer	-- Lay Person
11.	Thiru. S. Govindasamy, BABL, High Court, Chennai-1.	-- Lawyer
12.	Tmt. Arnold Saulina, MA MSW	-- Social Scientist

We approve the proposal to be conducted in its presented form.

Sd/Chairman & Other Members

The Institutional Ethics Committee expects to be informed about the progress of the study, and SAE occurring in the course of the study, any changes in the protocol and patients information / informed consent and asks to be provided a copy of the final report.

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE
CHENNAI-600 003

Member Secretary, Ethics Committee

KEY WORDS TO MASTER CHART

Age

1-3years- 1

3-6 years-2

6-10 years -3

>10 years 4

Sex

Male -1

-female -2

Family history

positive family history -1

Negative history-2

Initial presentation

Dka -1

Ndka-2

Presence of GAD antibodies

Positive-1

Negative -2

Presence of thyroid swelling -1

no thyroid swelling -2

sl.no	name		age				sex			family history			initial presentation			known dm	preci factor		non dka				thyroid swelling		GAD antibodies				insulin requirement		normothyriod	hypothyroid
		1-3yrs	3-6yrs	6-10yrs	above10yrs		male	female		yes	no		dka	ndka		no of epi	yes	no	incident	symptom	polyuria	polydipsia abd pain	wt loss	yes	no	yes	no					
1	rajkiran		Y			2	male		1		no	2		Y	2					y	y	y			no		no	2	11.9	1.7units	2	yes	
2	kavya		y			2		female	2		no	2	y		1					y	y	y			no		no	2	13.7	1unit	1	yes	
3	suchitra			y		3		female	2		no	2	y		1					y	y	y			no		no	2	11.5	1.8unit	2	yes	
4	swetha	y				1		female	2	yes		1		y	2					y	y	y			no	yes		1	10.6	.6units	1	yes	
5	chandru			y		3	male		1	yes		1	y		1					y	y	y			no	yes		1	7.8	1.9unit	2	yes	
6	karthick	y				1	male		1		no	2	y		1					y	y	y			no		no	2	9.3	1unit	1	yes	
7	anitha				y	4		female	2		no	2	y		1					y	y	y			no		no	2	6.5	1.5unit	2	yes	
8	surya				y	4	male		1		no	2	y		1					y	y	y			no	yes		1	7.8	1.4unit	2	yes	
9	abinaya		y			2		female	2		no	2	y		1					y	y	y			no		no	2	5	2.1unit	2	yes	
10	angel		y			2		female	2		no	2	y		1					y	y	y			no		no	2	10.3	1.1unit	2	yes	
11	silambarasi			y		3		female	2		no	2		y	2					y	y	y			no	yes		1	17.3	.5unit	1	yes	
12	thamman		y			2	male		1		no	2	y		1					y	y	y			no		no	2	7.1	3.1unit	2	yes	
13	arulmurugan		y			2	male		1		no	2	y		1					y	y	y			no	yes		1	15-Jan	1.6unit	2	yes	
14	sanjay			y		2	male		1	yes		1	y		1					y	y	y			no	yes		1	11.9	1.3units	2	yes	
15	sathish			y		3	male		1		no	2	y		1					y	y	y			no	yes		1	8	1.1units	2	yes	
16	hasmitha		y			2		female	2		no	2	y		1					y	y	y			no		no	2	11.2	1.8units	2	yes	
17	harini				y	4		female	2		no	2	y		1					y	y	y			no	yes		1	11-Jan	1.3units	2	yes	
18	nivaspandy		y			2	male		1		no	2			1					y	y	y			no		no	2	10	1.6unit	2	yes	
19	kalaiyarasan			y		3	male		1		no	2	y		1					y	y	y			no		no	2	10.7	1.3units	2	yes	
2o	sri			y		3		female	2		no	2	y		1					y	y	y			no	yes		1	6.3	2.25unit	2	yes	
21	akash				y	4	male		1	yes		1	y		1					y	y	y			no	yes		1	17.4	3.6units	2	yes	
22	madhyumitha	y				1		female	2		no	2	y		1					y	y	y			no	yes		1	9.5	.4 units	1	yes	
23	ashokkumar				y	4	male		1		no	2	y		1					y	y	y			no	yes		1	11.5	1.3units	2	yes	
24	sukumar				y	4	male		1		no	2	y		1					y	y	y			no	yes		1	14.8	1.7units	2	yes	
25	sivakami				y	4		female	2	yes		1	y		1					y	y	y			no	yes		1	14.5	1.9units	2	yes	
26	lavanya				y	4		female	2		no	2	y		1					y	y	y			no	yes		1	9.2	.6units	1	yes	
27	bavadharani				y	4		female	2		no	2		y	2			y		y	y	y			no		no	2	8.2	.44units	1	yes	
28	joshu franklin	y				1	male		1		no	2	y		1					y	y	y			no		no	2	8.3	3units	2	yes	
29	sreevishal			y		3	male		1		no	2		y	2					y	y	y			no	yes		1	13.6	1.2units	2	yes	
30	venkatesh				y	4	male		1		no	2	y		1					y	y	y			no	yes		1	8.6	1.9units	2	yes	
31	satheesh		y			2	male		1		no	2	y		1					y	y	y			no		no	2	12.3	1.6units	2	yes	
32	saranya			y		3		female	2	yes		1	y		1					y	y	y			no		no	2	16.9	.9units	1	yes	
33	sreesha				y	4	male		1		no	2		y	2					y	y	y			no	yes		1	10.3	1.4units	2	yes	
34	swathy		y			2		female	2		no	2	y		1					y	y	y			no		no	2	14.3	2.9units	2	yes	
35	veeramani			y		3	male		1		no	2		y	2					y	y	y			no		no	2	5.7	.6units	1	tes	
36	syed sherif			y		3	male		1		no	2		y	2					y	y	y			no		no	2	11.2	.9units	1	yes	
37	shylaja				y	4		female	2		no	2	y		1					y	y	y			no		no	2	8.9	1.4units	2	yes	
38	aruna		y			2		female	2		no	2		y	2					y	y	y			no		no	2	9.2	.7units	1	yes	
39	sabithra				y	4		female	2	yes		1		y	2					y	y	y			no		no	2	5.4	1.8units	2	yes	
40	shreja				y	4		female	2		no	2		y	2					y	y	y			no		no	2	5	1.1units	2	yes	
41	abinsree				y	4		female	2		no	2	y		1					y	y	y		yes	no		no	2	12.1	2.4units	2	yes	

42	aiswarya				y	4		female	2		no	2	y		1					y	y	y			no	yes		1	11.7	1unit	1	yes	
43	vignesh				y	4	male		1		no	2	y		1					y	y	y			no		no	2	6.3	1.5units	2	no	
44	divya		y			2		female	2	yes		1	y		1					y	y	y			no		no	2	11.7	1.4units	2	yes	
45	mohanapriya			y		3		female	2		no	2	y		1					y	y	y			no	yes		1	9.5	.8units	1	yes	
46	venkatkarthick			y		3	male		1	yes		1	y		1					y	y	y			no		no	2	15.7	1.45units	2	yes	
47	sivapriya		y			2	male		1		no	2	y		1					y	y	y			no		no	2	9.5	.86units	1	yes	
48	jamuna		y			2		female	2		no	2	y		1					y	y	y			no		no	2	15.7	1.45units	2	yes	
49	princy				y	4		female	2	yes		2	y		1					y	y	y			no	yes		1	11	1.6units	2	yes	
50	vinaykumar		y			2	male		1		no	2	y		1					y	y	y			no		no	2	11	1.2units	2	yes	